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(54) 3-[alpha-(3,5-di-t-butyl-4-hydroxyphenyl)-alkanoyl]pyrroles, their de-oxy analogs, and therapeutic

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uses thereof.

(57) 3-[ω -(3,5-Di-t-butyl-4-hydroxyphenyl)alkanoyl]pyrroles and their de-oxy analogs, for example, 3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole, 2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole and 3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole, are useful for the treatment of psoriasis or other allergic conditions such as conjunctivitis, bronchial asthma and inflammatory bronchial diseases; inflammatory bowel disease; inflammatory diseases; as analgesic and antipyretic agents; in bone diseases such as osteoporosis, periodontitis, tumor-related hypercalcemia, osteopetrosis, and Paget's Disease; and in ischemic heart disease including myocardial ischemia and myocardial infarction.

PATENTANWÄLTE

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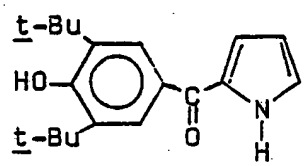
3-[ω-(3,5-DI-t-BUTYL-4-HYDROXYPHENYL)-ALKANOYL]PYRROLES, THEIR DE-OXY ANALOGS, AND THERAPEUTIC USES THEREOF

3-[ω-(3,5-Di-t-butyl-4-hydroxyphenyl)-alkanoyl]pyrroles, Their De-oxy Analogs, And Therapeutic Uses Thereof

The present invention relates to compounds having pharmacological activity, more specifically to non-steroidal anti-inflammatory agents, analgetic agents, anti-pyretic agents, anti-psoriatic agents, as agents against bone disorders, including bone degenerative and metabolic bone disorders, and as agents against ischemic heart disease including myocardial ischemia and myocardial infarction, and particularly to a series of 3-[ω-(3,5-di-t-butyl-4-hydroxyphenyl)alkanoyl]pyrroles and their de-oxy analogs.

The use of certain pyrroloyl compounds as non-steroidal anti-inflammatory agents is known. For example, U.S. Patent No. 4,418,074 (to Moore) describes:

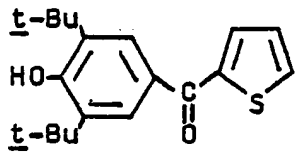


(Formula I)

2,6-di(t-butyl)-4-(2'-pyrroloyl)phenol

and reference is made to several other U.S. patents in which substitutions at the 4-position of 2,6-di(t-butyl)-phenols are taught, including: an N-substituted carboxamido group (4,128,664), an optionally substituted benzoyl group (4,124,725), an optionally substituted phenyl group (4,172,151), and optionally substituted thiophenyl groups (4,172,082).

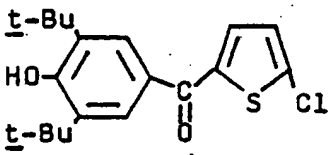
Other compounds having the di-t-butyl-hydroxyphenyl moiety have been proposed as anti-inflammatory agents, including:



(Formula II)

2,6-di-t-butyl-4-(2'-thenoyl)phenol

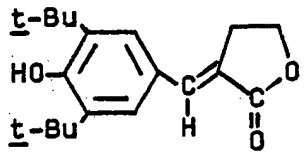
[Moore and Swingle, Agents and Actions, 12(5): 674-683 (1982)];



(Formula III)

2,6-di-t-butyl-4-(5'-chloro-2'-thenoyl)phenol

[Moore, Bell and Swingle, "SAR of Antioxidant-Antiinflammatory Agents: Di-t-Butyl Phenols and Other Series", 19th National Medicinal Chemical Symposium of the ACS, Tuscon, AZ, 151-154, June 17-21, 1984];

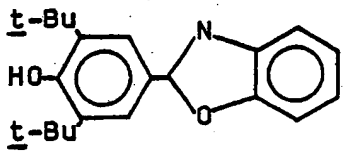


(Formula IV)

α-(3,5-di-t-butyl-4-hydroxy-benzylidine)-γ-butyrolactone

[Hidaka, et al., Ensho, 3(4): 511-512 (1983)];

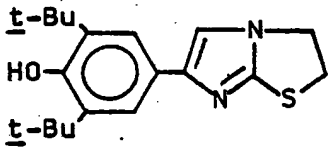
2,6-di-t-butyl-phenols with a heterocyclic group at the 4-position, such as:



(Formula V)

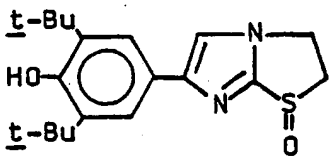
2-(3,5-di-t-butyl-4-hydroxyphenyl)benzoxazole

[Isomura, et al., Chem. Pharm. Bull., 31(9): 3168-3178 (1983)];



(Formula VI)

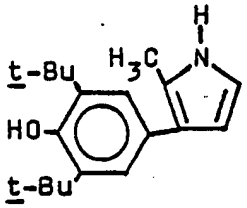
6-(3,5-di-t-butyl-4-hydroxyphenyl)-2,3-dihydroimidazo[2,1-b]thiazole,



(Formula VII)

6-(3,5-di-t-butyl-4-hydroxyphenyl)-2,3-dihydroimidazo[2,1-b]thiazole 1-oxide,

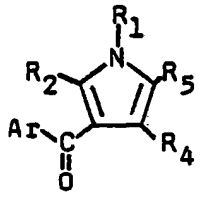
and the corresponding 1,1-dioxide [Isomura, et al., Chem Pharm. Bull., 31(9): 3179-3185 (1983)]; and



(Formula VIII)

3-(3,5-di-t-butyl-4-hydroxyphenyl)-2-methylpyrrole [Isomura, et al., Chem. Pharm. Bull., 32(1): 152-165 (1984)]. The compound of Formula VIII was, however, reported to be inactive.

U.S. Patent No. 3,644,631 (to Pachter, et al.) discloses the generic formula:



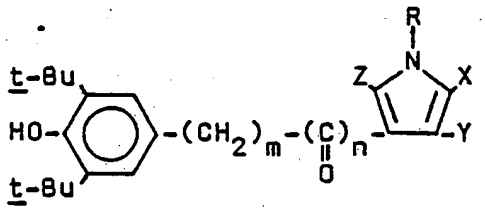
(Formula IX)

wherein, e.g., R_1 can be H, lower alkyl, or phenyl; R_2,R_4, and R_5 can be H, lower alkyl, or halo-; and Ar can be substituted aryl including tri-substituted by groups including lower alkyl or hydroxy. These compounds are proposed for anti-inflammatory uses. The disclosure, however, focuses on substitutions to the pyrrole; it does not encompass branched-chain-alkyl-substituted aryl groups, nor aryl groups with both alkyl and hydroxy substitutions.

It has been suggested that inhibition of the enzymes cyclooxygenase and lipoxygenase may be involved in the activity of anti-inflammatory agents. The involvement of antioxidant activity has also been suggested.

The use of non-steroidal anti-inflammatory drugs in the treatment of bone disorders has been described in the literature. Flurbiprofen has been suggested for use in the management of bone resorption disease [see, e.g., Williams et al., Flurbiprofen: A Potent Inhibitor of Alveolar Bone Resorption in Beagles, Science, 227, 640-642 (1985)]. Similar uses have been reported for naproxen, ketorolac, indomethacin and cycloheximide [see, Chin et al., Human Interleukin IL-1β, A More Powerful Inducer of Bone Demineralization Than IL-1-α, PTH or PGE_2 In Vitro, Fed. Proc., 45, 454 (1986)], and for thionaphthene-2-carboxylic acid [see, Johannesson et al., Thionapthene-2-Carboxylic Acid: A New Antihypercalcemic Agent, Endocrinology, 117(4) 1508-1511 (1985)].

3-[ω-(3,5-Di-t-butyl-4-hydroxyphenyl)alkanoyl]-pyrroles, their de-oxy analogs, and the pharmaceutically acceptable salts thereof, as represented by Formula X:



(Formula X)

wherein:

"t-Bu-" refers to $-C(CH_3)_3$, the tertiary butyl radical;

m is an integer from zero to three;

n is an integer from zero to one;

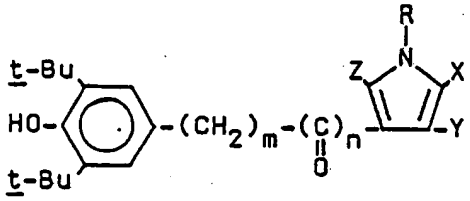
m+n is an integer from one to three;

R is H, lower alkyl, halo, carboxy lower alkylene, phenyl, benzyl, or a removable directing group; and

X, Y and Z are independently selected from H, lower alkyl, CF_3, halo, SCN, SR', SOR" and SO_2R" (wherein R' is H, aryl, lower alkyl or lower alkanoyl; and R" is lower alkyl or aryl);

are useful for the treatment of psoriasis or other allergic conditions such as conjunctivitis, bronchial asthma and inflammatory bronchial diseases, and inflammatory bowel diseases, inflammatory diseases by virtue of the fact that they inhibit cyclooxygenase, lipoxygenase and/or the generation of superoxide radical anion, as analgesic and antipyretic agents, in the treatment of bone diseases, such as osteoporosis, periodontitis, tumor-related hypercalcemia, osteopetrosis, and Paget's Disease, in the treatment of ischemic heart disease including myocardial ischemia and myocardial infarction, or are useful as intermediates for the synthesis of such compounds.

Compounds of Formula X'



(Formula X')

wherein:

"t-Bu-" refers to $-C(CH_3)_3$, the tertiary butyl radical;

m is an integer from zero to three;

n is an integer from zero to one;

m+n is an integer from one to three;

R is H, lower alkyl, carboxy lower alkylene, phenyl, or benzyl; and

X, Y and Z are independently selected from H, lower alkyl, CF_3, halo, SCN, SR', SOR" and SO_2R"

(wherein R' is H, aryl, lower alkyl or lower alkanoyl; and R" is lower alkyl or aryl);

are useful for the treatment of psoriasis or other allergic conditions such as conjunctivitis, bronchial asthma and inflammatory bronchial diseases, inflammatory bowel diseases, inflammatory diseases, and as analgesic and antipyretic agents, by virtue of the fact that they inhibit cyclooxygenase, lipoxygenase, the generation of superoxide radical anion and/or lower thromboxane levels. It has also been discovered that the compounds of Formula X' are useful in the treatment of bone diseases, such as osteoporosis, periodontitis, tumor-related hypercalcemia, osteopetrosis, and Paget's Disease and in the treatment of ischemic heart disease including myocardial ischemia and myocardial infarction.

One aspect of the present invention entails the compounds having the structure of Formula X. Another aspect of the invention entails pharmaceutical formulations of such compounds with carriers.

Yet another aspect of the invention entails processes for preparing compounds having the structure of Formula X.

Still another aspect of this invention is a method of treating pain, inflammation, pyrexia, and ischemic heart disease including myocardial ischemia and myocardial infarction which comprises administering an effective amount of a compound having the structure of Formula X'.

Another aspect of the present invention is a method for treating bone diseases, such as osteoporosis, periodontitis, tumor-related hypercalcemia, osteopetrosis, and Paget's Disease, by administering an effective amount of a compound having the structure of Formula X' or a pharmaceutical formulation thereof.

Definitions

The following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

As used herein, the term "alkyl" refers to an alkane radical containing only carbon and hydrogen, which is fully saturated and may be branched or straight chain.

As used herein, the term "lower alkyl" refers to an alkane radical of one to four carbon atoms, and which may be a branched or straight chain radical. This term is further exemplified by such radicals as methyl, ethyl, propyl, isopropyl, butyl, isobutyl and t-butyl.

As used herein, the term "lower alkylene" refers to a divalent fully saturated hydrocarbon radical of one to four carbon atoms, and which may be branched or straight. This term is further exemplified by such radicals as methylene, ethylene, propylene, isopropylene, butylene and isobutylene.

As used herein, the term "lower alkanoyl" refers to an alkyl carbonyl radical of the formula RC(O)-, where R is lower alkyl. This term is further exemplified by such radicals as acetyl, propanoyl and butanoyl.

As used herein, the term "carboxy lower alkylene" refers to a carboxy alkylene radical of the formula HOOC-R'-, where R' is a branched or a straight chain alkylene radical of one to three carbon atoms. This term is further exemplified by such radicals as carboxymethyl, carboxyethyl, 3-carboxypropyl and 1-methyl-2-carboxyethyl.

As used herein, the term "aryl" refers to an organic radical derived from an aromatic hydrocarbon by the removal of one hydrogen atom from the aromatic ring. The term is exemplified by phenyl, naphthyl or anthracenyl.

As used herein, the term "aryl lower alkyl" refers to a radical of the formula Ar-R-, where Ar is aryl and R is alkylene, as defined above. The term is exemplified by benzyl and phenethyl.

As used herein, the terms "t-butyl" and "t-Bu-" refer to $-C(CH_3)_3$, the tertiary butyl radical.

As used herein, the term "halo" refers to bromo, iodo, fluoro, and chloro.

As used herein, the term "removable directing group" refers to a group that directs the acylation by an acid halide to the 3 (or beta) position of a pyrrole, and is removable thereafter under conditions that do not affect other substituents on the molecule. Such groups include electron withdrawing groups such as arylsulfonyl (e.g., phenylsulfonyl), aryl lower alkylsulfonyl (e.g., benzylsulfonyl), lower alkyl arylsulfonyl (e.g., tolylsulfonyl), lower alkylsulfonyl (e.g., ethylsulfonyl), and benzoyl. Presently preferred are arylsulfonyl, aryl lower alkylsulfonyl, lower alkyl arylsulfonyl and lower alkylsulfonyl, especially arylsulfonyl, and particularly N-phenylsulfonyl.

The compounds of Formula X are described herein as 3-[ω-(3,5-di-t-butyl-4-hydroxyphenyl)alkanoyl]pyrroles and their de-oxy analogs. This is intended to refer to an ω-(3,5-di-t-butyl-4-hydroxyphenyl)alkanoyl or an ω-(3,5-di-t-butyl-4-hydroxyphenyl)alkyl substitutuent at the beta position of the pyrrole ring. Thus, some substituted compounds of Formula X may be named as 4-[ω-(3,5-di-t-butyl-4-hydroxyphenyl)alkanoyl]- or 4-[ω-(3,5-di-t-butyl-4-hydroxyphenyl)alkyl]pyrroles, depending upon the nature and placement of other substituents on the pyrrole ring, for example, 2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole.

A pharmaceutically acceptable salt may be any salt derived from an inorganic or organic base which retains the activity of the parent compound and is non-toxic to a

subject. Salts may be derived from such inorganic ions as sodium, potassium, lithium, ammonium, calcium, magnesium, ferrous, zinc, copper, manganous, aluminum, ferric, manganic salts and the like. Particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Pharmacetically acceptable salts derived from organic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropyl amine, trimethyl amine, diethyl amine, triethyl amine, tripropyl amine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, tromethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylendiamine, glucosamine, methylglucamine, theobromine, purines, piperizine, piperidine, n-ethylpiperidine, polyamine resins, and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, piperidine, tromethamine, dicyclohexylamine, choline and caffeine.

As used herein, the term "treatment" or "treating" means any treatment of a disease in a mammal, including:

(i) preventing the disease, that is, causing the clinical symptoms of the disease not to develop;

(ii) inhibiting the disease, that is, arresting the development of clinical symptoms; and/or

(iii) relieving the disease, that is, causing the regression of clinical symptoms.

As used herein, the term "effective amount" means a dosage sufficient to provide treatment for the disease state being treated. This will vary depending on the patient, the disease and the treatment being effected.

As used herein, the term "q.s." means adding a quantity sufficient to achieve a stated function, e.g., to bring a solution to the desired volume (i.e., 100%).

Synthesis of the Compounds

3-[ω-(3,5-Di-t-butyl-4-hydroxyphenyl)alkanoyl]-pyrroles and their de-oxy analogs having the general structure of Formula X can be synthesized by a variety of reaction sequences, for example, in the manner shown in Sections A-N below.

Typically, the compounds of this invention can be prepared from an acid halide and an appropriately substituted or unsubstituted pyrrole starting material having a removable directing group, in accordance with the reaction sequences described below. An electron-attracting substituent on the 2 position of a pyrrole could be used to direct addition of the acid halide to the 3 position of the pyrrole. Compounds having strongly electron-attracting substituents (such as, SOR", and SO_2R") are prepared from the unsubstituted 3,5-di-t-butyl-4-hydroxyphenyl -alkanoyl or -alkyl pyrrole at the end of the process, as described more fully below. On the other hand, the alkyl-substituted pyrroles (other than N-alkyl) and the trifluoromethyl-substituted pyrroles must be prepared using an alkyl- or trifluoromethyl-substituted starting material.

In the following preparations, unless specified to the contrary, the reactions take place at atmospheric pressure over a temperature range from about 0°C to about 100°C, more preferably from about 10°C to about 50°C, and most preferably at about room temperature.

A. Preparation of Intermediates

Referring to Reaction Scheme A, compound "C" is prepared by a Friedel-Crafts reaction between an acid halide "A" and an N-(removable directing group)pyrrole "B". As used in Reaction Scheme A, substituents X, Y and Z on "B" and "C" are not strongly electron attracting (e.g., they can be H, lower alkyl, CF_3, halo, SCN or SR').

The acid halides "A" [e.g., 3,5-di-t-butyl-4-hydroxybenzoyl chloride, 3,5-di-t-butyl-4-hydroxyphenylacetyl chloride or 3-(3,5-di-t-butyl-4-hydroxyphenyl)-propanoyl chloride; preferably 3,5-di-t-butyl-4-hydroxybenzoyl chloride] are obtained by halogenation of a corresponding acid (e.g., 3,5-di-t-butyl-4-hydroxybenzoic acid - available from Aldrich Chemical Company), for example by contacting it with thionyl chloride, as is known in the art.

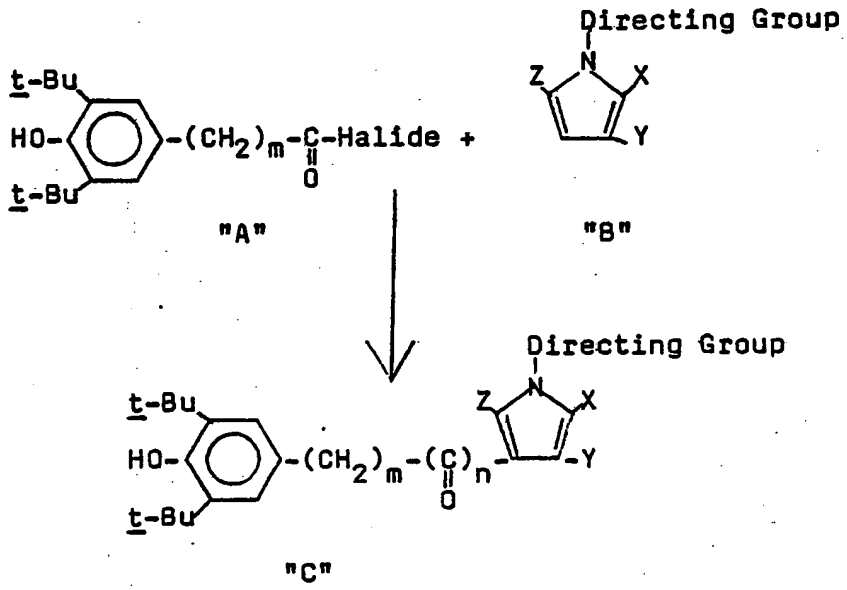
The N-(removable directing group)pyrroles "B" (e.g., N-phenylsulfonylpyrrole, N-p-tolylsulfonylpyrrole, N-methylsulfonylpyrrole or N-phenylsulfonyl-2,5-dimethylpyrrole; preferably N-phenylsulfonylpyrrole) are also obtained by methods known in the art. For example, pyrrole, an alkyl-substituted pyrrole, a trifluoromethyl-substituted pyrrole, or a halo-substituted pyrrole [e.g., 2,5-dimethylpyrrole (available from Aldrich Chemical Company), 2-trifluoromethylpyrrole (prepared as described in Section E, below) or 2-chloropyrrole (prepared by halogenation as described in Section L, below)] is contacted with either (a) potassium in tetrahydrofuran ("THF") and then with the chloride of a removable directing group (e.g., benzylsulfonyl chloride or tolylsulfonyl chloride), or (b) sodium hydride in dimethylformamide ("DMF") and then with the chloride of a removable directing group (e.g., phenylsulfonyl chloride).

Both "A" and "B" are dissolved in an organic solvent that is inert under the conditions of the reaction (e.g., nitrobenzene, dichloromethane, dichloroethane or nitromethane; preferably dichloroethane), in the presence of an excess of a Lewis acid catalyst (e.g., aluminum trichloride, boron trifluoride, stannic chloride or ferric chloride; preferably aluminum trichloride). The Friedel-Crafts reaction takes place over a period of about 30 minutes to about 24 hours, more preferably about

45 minutes to about 4 hours, and most preferably about 1.5 hours. The resulting product "C" is conventionally isolated and purified.

For example, using 3,5-di-t-butyl-4-hydroxybenzoyl chloride and N-phenylsulfonylpyrrole in the above general reaction yields N-phenylsulfonyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (a compound according to Formula X wherein: m is 0; n is 1; R is $SO_2\phi$; and X, Y and Z are each H). Likewise, using 3,5-di-t-butyl-4-hydroxybenzoyl chloride and N-phenylsulfonyl-2,5-dimethylpyrrole in the above general reaction yields N-phenylsulfonyl-2,5-dimethyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (a compound according to Formula X wherein: m is 0; n is 1; R is $SO_2\phi$; Y is H; and X and Z are each CH_3).

Reaction Scheme A

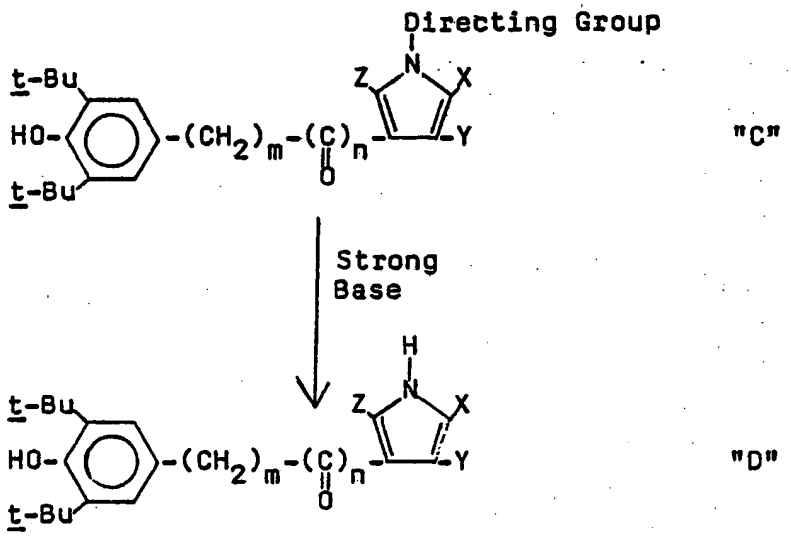


B. Preparation of Parent Compound(s)

As shown in Reaction Scheme B (where X, Y and Z can be H, lower alkyl, CF_3, halo, SCN or SR') the removable

directing group is removed from the intermediates represented by the formula "C". This is done by dissolving a compound according to formula "C" in an organic solvent that is miscible with water and is inert under the conditions of the reaction (e.g., dioxane, methanol, nitromethane, THF, ethanol, isopropanol or acetonitrile; preferably dioxane and methanol) and adding a strong base (e.g., NaOH, KOH, or LiOH; preferably NaOH) as an aqueous solution. The reaction takes place at elevated temperatures of 40-100°C, e.g., on a steam bath, over a period of about 5 minutes to about 1 hour, more preferably about 20 minutes. The resulting products, compounds according to formula "D", are conventionally isolated and purified.

Reaction Scheme B



For example, using N-phenylsulfonyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole in this general reaction yields 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (a

compound according to Formula X wherein: m is 0; n is 1; R is H; and X, Y and Z are each H). Likewise, using N-phenylsulfonyl-2,5-di-methyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole in the above general reaction yields 2,5-dimethyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole (a compound according to Formula X wherein: m is 0; n is 1; R is H; Y is H; and X and Z are each methyl).

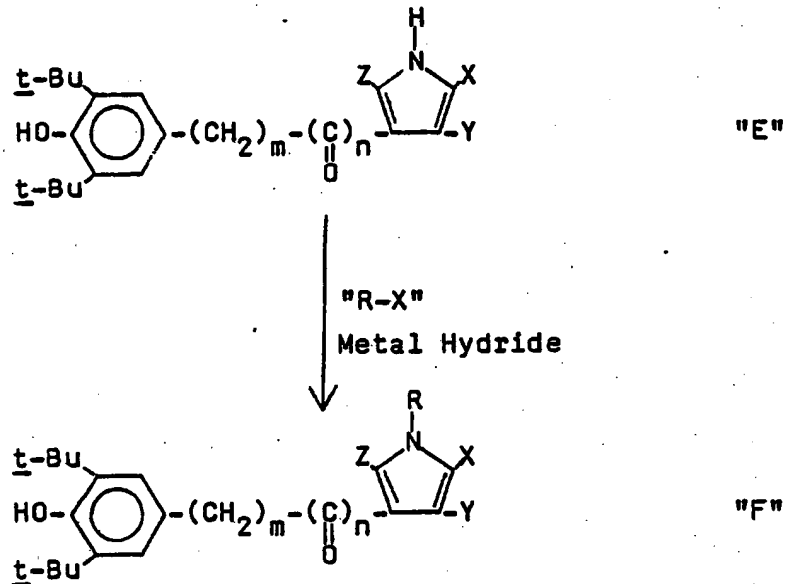
C. Alkylation/Benzylation of the Pyrrole's Nitrogen

As shown in Reaction Scheme C, conversion of the compounds according to formula "E" (i.e., compounds of Formula X where R is hydrogen) to the corresponding compounds according to formula "F" where R is lower alkyl or benzyl is effected by contacting the compounds "E" [dissolved in a solvent inert under the conditions of the reaction, e.g., DMF, THF, N-methylpyrrolidone, or dimethylsulfoxide ("DMSO"); preferably DMF] with about 1 to 4, preferably about 2, molar equivalents of an alkali metal hydride (e.g., KH, NaH, or LiH; preferably NaH) for about 15 minutes to about 6 hours, preferably about 1 hour.

This is followed by the addition of about 1 to 5, preferably about 1.1, molar equivalents of an alkylating agent ["R-X" where R is alkyl, benzyl or carboxy(lower alkyl) and X is a leaving group] dissolved in the same solvent. In particular, "R-X" can be either a lower alkyl halide (e.g., methyl iodide, ethyl bromide, propyl iodide, butyl chloride), an optionally ring-substituted benzyl halide (e.g., benzyl chloride, benzyl iodide, benzyl bromide or benzyl fluoride), or a halogenated alkanoic acid or ester (e.g., chloropropionic acid, ethyl chloroacetate or preferably bromoacetic acid; these require an additional molar equivalent of the alkali metal hydride described above).

A temperature range from about -10°C to about 50°C, preferably about room temperature can be used. The reaction takes place over a period of about 15 minutes to about 24 hours, preferably over a period of about 30 minutes to about 3 hours, and most preferably about 1 hour. The resulting product "F", in which R is lower alkyl, benzyl or carboxy lower alkylene, is conventionally isolated and purified.

Reaction Scheme C



For example, using 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole as compound "E" in this general reaction together with ethyl bromide as "R-X" yields N-ethyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (a compound according to Formula X wherein: m is 0; n is 1; R is ethyl; and X, Y and Z are each H).

Likewise, using 2,5-dimethyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole as compound "E" in this general reaction with benzyl chloride as "R-X" yields N-benzyl-

2,5-dimethyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (a compound according to Formula X wherein: m is 0; n is 1; R is benzyl; Y is H; and X and Z are each methyl).

Similarly, using 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole as compound "E" in this general reaction with bromoacetic acid as "R-X" and 3 molar equivalents of NaH yields N-carboxymethyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (a compound according to Formula X wherein: m is 0; n is 1; R is CH_2COOH; and X, Y and Z are each H).

D. Alkylation of the Pyrrole Starting Material

The compounds of Formula X wherein X, Y and/or Z are lower alkyl are prepared by a Friedel-Crafts reaction, such as that described in Sections A & B above, between an acid halide and an N-(removable directing group)-(alkyl-substituted)pyrrole (e.g., N-phenylsulfonyl-2,5-dimethylpyrrole, N-phenylsulfonyl-3-ethylpyrrole or N-phenylsulfonyl-2-propylpyrrole, which are made according to methods commonly known in the art).

The N-(removable directing group)-alkyl-substituted pyrrole is prepared as described in Section A above, and is then used as compound "B" in the Friedel-Crafts reaction to give the desired end products, using the reaction times and conditions as described above.

E. Trifluoromethylation of the Pyrrole Starting Material

The compounds of Formula X wherein X, Y and/or Z are CF_3 are prepared by a Friedel-Crafts reaction, such as that described in Sections A & B above, between an acid halide and an N-(removable directing group)-(trifluoromethyl-substituted)pyrrole [e.g., N-phenylsulfonyl-2-(trifluoromethyl)pyrrole].

The pyrrole starting material may be obtained by photochemical trifluoromethylation of a pyrrole, e.g., by following the procedure of Kobayashi, Y., et al.,

Chem. Pharm. Bull., 26(4) 1247-1249 (1978). This can be accomplished by sealing CF_3I and the pyrrole in a silica tube under vacuum and irradiating the sealed tube with a low pressure mercury lamp for about 2 days. After irradiation, the gaseous products are degassed at room temperature and the residue is distilled with a vacuum line, yielding the desired (trifluoromethyl)pyrrole.

F. Introduction of a Thiocyano Group on the Pyrrole Nucleus

The compounds of Formula X wherein X, Y and/or Z are -SCN, are prepared by contacting an appropriate pyrrol-3-yl ketone (i.e., a compound according to Formula X wherein X, Y and/or Z are H and R is not a removable directing group) with thiocyanogen (prepared from an alkali metal thiocyanate, such as potassium thiocyanate and bromine at 0°C in methanol) in an organic solvent inert under the conditions of the reaction (e.g., anhydrous DMF, a lower alcohol such as methanol or ethanol, or methylene chloride). The molar ratio of thiocyanogen to starting material is about 1 - 10 molar equivalents, preferably about 1:1 for the mono-substituted pyrroles and in increasing ratios for the di- and tri-substituted pyrroles. The reaction takes place over a period of about 10 minutes to about 10 hours, more preferably about 30 minutes to about 4 hours, and most preferably over 1.5 hours. A temperature range from about -100°C to about 40°C can be used, preferably about -35°C. The end products are separated and purified by conventional means.

For example, using 3-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole in this general reaction together with one molar equivalent of thiocyanogen yields 2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (a compound according to Formula X wherein: m is 0; n is 1; R is H; and X is SCN; and Y and Z are each H).

G. Introduction of a Mercapto Group on the Pyrrole Nucleus

The compounds of Formula X wherein X, Y and/or Z are mercapto are prepared by dissolving a mono-, di- or tri-thiocyanopyrrole (prepared as described in Section F) in a protic solvent (e.g., EtOH, PrOH, t-BuOH, THF-H_2O or preferably MeOH). A methanolic solution of an inorganic base (e.g., LiOH, KOH, or preferably NaOH) is added slowly, maintaining the temperature of the reaction mixture between about -30°C to about 5°C, preferably about -10°C. After mechanical agitation (e.g., stirring) for a period of about 5 minutes to about 3 hours, preferably about 1 hour, an excess of an acidifying agent (e.g., 20% HCl) is added, yielding the desired mercaptopyrrole, which is purified and isolated by conventional means.

For example, using 2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole in this general reaction together with one molar equivalent of potassium hydroxide yields 2-mercapto-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole (a compound according to Formula X wherein: m is 0; n is 1; R is H; and X is SH; and Y and Z are each H).

H. Introduction of an Alkylthio Group on the Pyrrole Nucleus

The compounds of Formula X wherein X, Y and/or Z are lower-alkylthio, are prepared by contacting a mono-, di- or tri-thiocyanopyrrole (prepared as described in Section F) with an alkyl halide ("R-X", as defined earlier; preferably an alkyl iodide such as methyl iodide or ethyl iodide) in the corresponding protic solvent ("R-OH", e.g., MeOH, EtOH, PrOH; preferably MeOH). Alternatively, t-BuOH or THF-H_2O can be used as the solvent. The molar ratio of alkyl halide to starting material will vary (i.e., 1:1, 2:1 or 3:1) depending upon whether a

mono-, di-, or tri- substituted product is desired. The reaction mixture is then cooled to about -30°C to about 5°C, preferably about -5°C, and a methanolic solution of an inorganic base (e.g., LiOH, KOH, or preferably NaOH) is added. The mixture is brought to about 0°C to about 40°C, preferably about room temperature, and the mixture is allowed to react for a period of about 5 minutes to about 4 hours, preferably about 30 minutes. The solution is neutralized with dry-ice. The end products are purified and isolated by conventional means.

For example, using 2,3-dithiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole in this general reaction together with two molar equivalents of methyl iodide yields 2,3-dimethylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (a compound according to Formula X wherein: m is 0; n is 1; R is H; and Z is H; and X and Y are each SCH_3).

Alternatively, the compounds of Formula X where X, Y and/or Z are lower-alkylthio may be prepared by contacting an acylated pyrrole (dissolved in a solvent such as DMF) with a solution of an alkyl or aryl sulfenyl chloride, previously prepared from a mixture of an alkyl or aryl disulfide (e.g., methyl disulfide) and sulfuryl chloride in an inert organic solvent (e.g., CCl_4, $CHCl_3$ or CH_2Cl_2). The molar ratio of sulfenyl chloride to starting material will vary (i.e., 1:1, 2:1 or 3:1) depending upon whether a mono-, di-, or tri-substituted product is desired. The reaction takes place in about 30 minutes to about 4 hours, preferably about 1 hour. The end products are purified and isolated by conventional means.

I. Introduction of a Lower-Alkanoylthio Group on the Pyrrole Nucleus

The compounds of Formula X wherein X, Y and/or Z are lower-alkanoylthio, are prepared by contacting a mono-, di- or tri-thiocyanopyrrole (prepared as described in Section F) with an alkali metal acetate (e.g., potassium acetate, or preferably sodium acetate) and dissolving in an alkanoic acid (e.g., propanoic acid, or preferably acetic acid) and an alkanoic anhydride (e.g., propionic anhydride, or preferably acetic anhydride). With vigorous mechanical agitation (e.g., stirring), a strong reducing agent, preferably zinc dust, is added. The reaction mixture is neutralized with ice water. The mixture is allowed to react for a period of about 30 minutes to about 8 hours, preferably about 3 hours. The end product is isolated and purified by conventional means.

For example, using 2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole in this general reaction together with one molar equivalent each of sodium acetate, acetic acid, acetic anhydride and zinc dust, yields 2-acetylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole (a compound according to Formula X wherein: m is 0; n is 1; R is H; and X is SAc; and Y and Z are each H).

J. Introduction of an Alkylsulfinyl Group on the Pyrrole Nucleus

The compounds of Formula X wherein X, Y and/or Z are $-SOR''$, are prepared by the oxidation of an appropriate alkylthiopyrrol-3-yl ketone (prepared as described in Section H), which is carried out with one molar equivalent of an oxidizing agent (e.g., 30% hydrogen peroxide, peracetic acid, or preferably m-chloroperbenzoic acid) for each alkylthio group on the starting molecule, in an organic solvent inert under the

conditions of the reaction (e.g., $CHCl_3$, CCl_4, acetone or preferably dichloromethane). The reaction takes place over a period of about 10 minutes to about 2 hours, more preferably 20 minutes to about 1 hour, and most preferably over about 30 minutes after the addition of the oxidizing agent. A temperature range from about -30°C to about 50°C, more preferably from about -20°C to about 10°C, and most preferably 0°C may be used. The end products are isolated and purified by conventional means.

For example, using 2,5-dimethylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole in this general reaction together with two molar equivalents of m-chloroperbenzoic acid yields 2,5-dimethylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (a compound according to Formula X wherein: m is 0; n is 1; R is H; Y is H; and X and Z are each $SOCH_3$).

K. Introduction of an Alkylsulfonyl Group on the Pyrrole Nucleus

The compounds of Formula X wherein X, Y and/or Z are SO_2R'', are prepared by the oxidation of an appropriate alkylsulfinylpyrrol-3-yl ketone (prepared as described in Section J), which is carried out with one molar equivalent of an oxidizing agent (preferably m-chloroperbenzoic acid) for each alkylsulfinyl group on the starting molecule, in an inert organic solvent (e.g., dichloromethane). Alternatively, the reaction can be carried out starting with an appropriate alkylthiopyrrol-3-yl ketone (prepared as described in Section H), with two molar equivalents of oxidizing agent per -SR'. The reaction takes place over a period of about 10 minutes to about 2 hours, more preferably 20 minutes to about 1 hour, and most preferably over about 30 minutes after the addition of the oxidizing agent. The end products are purified by conventional means.

For example, using 2-methylsulfinyl-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxo-ethyl]pyrrole in this general reaction together with one molar equivalent of m-chloroperbenzoic acid yields 2-methylsulfonyl-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxo-ethyl]pyrrole (a compound according to Formula X wherein: m is 1; n is 1; R is H; and X is SO_2CH_3; and Y and Z are each H).

L. Introduction of a Halo Group on the Pyrrole Nucleus

As an alternative to starting with the halogenated pyrroles as described in Sections A & B above, the compounds of Formula X wherein X, Y and/or Z are halo and the other substituents are as described, can also be prepared by the halogenation of an appropriate pyrrole (such as a compound according to Formula X in which X, Y and/or Z is hydrogen and the other substituents are as described above). The reaction is carried out with a halogenating agent in an organic solvent that is inert under the conditions of the reaction (e.g., anhydrous methylene chloride, carbon tetrachloride, trichloromethane, THF or other ether solvents; preferably anhydrous methylene chloride or THF). The molar ratio of halogenating agent to starting material will vary (e.g., 1:2, 1:1, 2:1 or 3:1) depending upon whether a mono-, di-, or tri- substituted end product is desired. The end products are purified and isolated by conventional means. Alternatively, the starting material may be reacted with in excess of 4:1 molar equivalents of halogenating agent to form a stable tetrahalo intermediate, followed by dehalogenation of the N-halo substituent.

The ratios of mono-, di-, or tri- substituted end products can be varied depending on the ratio of halogenating agent to starting material. For example, if a ratio of 1:2 halogenating agent:unsubstituted compound

is used at room temperature, a larger percentage of the 2-halo- and 2,3-dihalo- compounds of formula X' are prepared. This ratio in the end product mixture will, however, depend upon the halogenating agent and conditions used, as described in greater detail below.

To prepare the compounds of Formula X where the substituents X, Y and/or Z are chloro, the halogenating agent is, e.g., elemental chlorine, N-chlorosuccinimide, 1,3-dichloro-5,5-dimethylhydantoin ("Halane") or sulfuryl chloride; preferably sulfuryl chloride for polychloro compounds and Halane for the compound where only X is chloro. The reaction takes place over a period of about 10 minutes to about 4 hours, but can be run for upwards of 100 hours. A preferable reaction time is from about 20 minutes to about 1 hour, and most preferably about 30 minutes. Using two molar equivalents of Halane as the halogenating agent, the reaction is carried out at a temperature from about -20°C to about 10°C, preferably at about -10°C, for a period of about 90 minutes, resulting predominantly in a 2-chloro compound according to formula X (where X is chloro, and Y and Z are hydrogen). Proceeding via the tetrachloro intermediate requires cooling the initial reactants to about -50 to about -100°C, preferably about -70°C, and allowing the reaction to run for about 6 to about 24 hours, preferably about 20 hours; this is followed by removal of the N-chloro substituent by treatment with a dehalogenating agent, such as a metal halide (e.g., potassium iodide) and a metal sulfite (e.g., sodium sulfite).

For example, using 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole in this general reaction together with two molar equivalent of Halane as the halogenating agent at -10°C for 90 minutes yields 2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (a compound according to Formula X wherein: m is 0; n is 1; R is H; X is Cl; and Y and Z are each H).

Using 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole in this general reaction together with over four molar equivalents of sulfuryl chloride as the halogenating agent yields 1,2,4,5-tetrachloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (a compound according to Formula X wherein: m is 0; n is 1; and R, X, Y and Z are each Cl). Treatment of this tetrachloro intermediate with potassium iodide and sodium sulfite in water yields 2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (a compound according to Formula X wherein: m is 0; n is 1; R is H; and X, Y and Z are each Cl).

In a presently preferred process for making 2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, a mixture of 2-chloro and polychloro compounds obtained by following one of the above-described procedures is partitioned between about a 50:15 mixture of a chlorinated solvent (such as 1,1,1-trichloroethane or methylene chloride; preferably methylene chloride) and an aqueous base [preferably 1 to 2 molar equivalents (based on moles of the compound) of sodium hydroxide in water] by stirring at about room temperature for about 2 to 48 hours, preferably about 24 hours, after which the organic phase is isolated, and worked up in the usual manner (e.g., washed with water, dried over a suitable dessicant, evaporated *in vacuo*, and crystallized, e.g., from acetonitrile and acetone/hexane).

Polychloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrroles (where Y and Z, X and Z, or X, Y and Z are chloro), for example, those remaining in the aqueous phase from the above-described partition or a mixture obtained by one of the other foregoing procedures, can be converted to yield additional 2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole (where X is Cl) by heating to about 45 to 60°C, preferably about 50 to 55°C, with acetic acid in the presence of zinc. This serves to selectively remove the

chlorine substituent from the 5 (or Z) position, leaving the 2-chloro and 2,3-dichloro analogs, which are worked up in the usual manner (washing, drying, evaporating in vacuo, optionally percolating through or chromatographing on silica gel, and crystallizing, e.g., from acetone/hexane) and which can be separated by the above-described partitioning method.

To prepare the compounds of Formula X where the substituents X, Y and/or Z are bromo, the halogenating agent is, e.g., N-bromosuccinimide or preferably elemental bromine. The reaction takes place over a period of about 30 minutes to about 4 hours, more preferably about 45 minutes to about 2 hours, and most preferably about 1 hour. A temperature range of about -100°C to about -50°C, preferably about -70°C may be used.

For example, using N-benzyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole in this general reaction together with two molar equivalents of elemental bromine as the halogenating agent yields N-benzyl-2,3-dibromo-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (a compound according to Formula X wherein: m is 0; n is 1; R is benzyl; X and Y are Br; and Z is H).

To prepare the compounds of Formula X where the substituents X, Y and/or Z are iodo, the halogenating agent is, e.g., iodosuccinimide or preferably elemental iodine. The reaction takes place at atmospheric pressure over a period of about 30 minutes to about 4 hours, more preferably about 45 minutes to about 2 hours, and most preferably about 1 hour.

For example, using N-methyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole in this general reaction together with one molar equivalent of elemental iodine as the halogenating agent yields N-methyl-2-iodo-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (a compound according to Formula X wherein: m is 0; n is 1; R is methyl; X and Y are H; and Z is I).

M. Reduction of Oxo Pyrroles

Compounds of Formula X where n is 0 can be prepared by the reduction of a 3-[ω-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxo-alkyl]pyrrole (e.g., a compound according to Formula X wherein n is 1) by contacting it with an excess (about 8:1 molar equivalents) of a strong reducing agent [e.g., lithium borohydride, sodium borohydride, or preferably lithium aluminum hydride ("LAH")] in an ethereal solvent (e.g., ether, dioxane or preferably THF). The reaction takes place in a temperature range from about 20°C to about 100°C, more preferably from about 40°C to about 80°C, and most preferably at about 65°C (or the reflux temperature for the solvent being used). The reaction takes place over a period of about 1 to 10 hours, more preferably 2 to 6 hours, and most preferably 4 hours. The product is purified and isolated by conventional means.

For example, using 2-methylsulfonyl-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxo-ethyl]pyrrole in this general reaction together with eight molar equivalents of LAH yields 2-methylsulfonyl-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)ethyl]pyrrole (a compound according to Formula X wherein: m is 2; n is 0; R is H; and X is SO_2CH_3; and Y and Z are each H). Likewise, using 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole in this general reaction together with eight molar equivalents of LAH yields 3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole (a compound according to Formula X wherein: m is 1; n is 0; R is H; and X, Y and Z are each H).

Alternatively, the compounds of Formula X where n is 0 can be prepared according to general reactions described in Sections C-E (i.e., excepting the electron withdrawing group-substituted pyrroles) using a 3-[ω-(3,5-di-t-butyl-4-hydroxyphenyl)alkyl]pyrrole [e.g., 3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole] as the starting material, which is prepared as described above.

N. Preparation of the Pharmaceutically Acceptable Salts

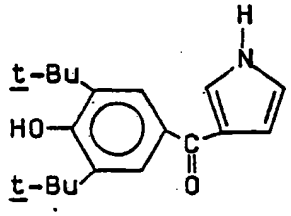
The pharmaceutically acceptable salts are formed on any or a combination of the following acidic sites in the compounds of Formula X, including the hydroxy radical of the phenol, the N-hydrogen of the pyrrole when R is hydrogen, the carboxyl when R is carboxy lower alkylene, or the hydrogen of -SH when X, Y and/or Z is mercapto.

In general, these salts are formed by dissolving a compound of Formula X in a solvent that is inert under the conditions of the reaction (e.g., a protic solvent such as aqueous alcohol, alcohol, or a dipolar aprotic solvent such as acetonitrile, dimethylformamide or dimethylsulfoxide; preferably ethanol or aqueous ethanol for inorganic bases; and for the organic bases, e.g., methylene chloride) and contacting the dissolved compound with one molar equivalent of the chosen inorganic ion or organic base, as described previously, for each salt forming site to be reacted. The reaction typically takes place over a period of about 5 minutes to about 2 hours, preferably about 30 minutes.

As is well known in the art, the salts, once formed, may be interconverted with other salts or released to form the free compound.

Preferred Compounds

A presently preferred compound is 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole [or 2,6-di(t-butyl)-4-(3-pyrroloyl)phenol], as shown in Formula XI).

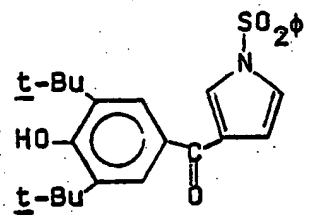


(Formula XI)

3-(3,5-Di-t-butyl-4-hydroxybenzoyl)pyrrole is, e.g., both an active anti-inflammatory agent and an intermediate for synthesizing other compounds according to Formula X.

Other presently preferred compounds include: 2-chloro-4-(3,5-di-t-butyl-4-hydroxbenzoyl)pyrrole; 2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and 2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole.

As shown in Sections A & B above, compound "D" is prepared through an intermediate "C". N-Phenylsulfonyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (shown in Formula XII) is a presently preferred N-(removable directing group)-substituted intermediate compound.



(Formula XII)

Another preferred intermediate is 1,2,4,5-tetrachloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole.

Preferred Processes of the Invention

The compounds of the present invention can be prepared according to the following last steps.

A preferred process for preparing the compounds of the invention involves a Friedel-Crafts reaction wherein a 3,5-di-t-butyl-4-hydroxyphenyl acid halide is directed to attach to the 3-position of pyrrole. A removable directing group (such as a alkylsulfonyl, phenylsulfonyl or tolylsulfonyl) is substituted on the pyrrole's nitrogen atom before the Friedel-Crafts reaction, and is later removed. The Friedel-Crafts reaction is also

performed with an alkyl-, a trifluoromethyl- or a halo-substituted pyrrole to give the corresponding alkyl-, trifluoromethyl- or halo-substituted end product of Formula X.

Other substituted compounds can be prepared as follows:

alkylation of the pyrrole's nitrogen;

carboxyalkylation of the pyrrole's nitrogen;

halogenation of the 2, 3 and/or 5 carbon atoms of the pyrrole;

reduction of the N-halo of a 1,2,4,5-tetrahalo-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole;

thiocyanogenation of the 2, 3 and/or 5 carbon atoms of the pyrrole;

thiocyanogenation of the 2, 3 and/or 5 carbon atoms of an N-substituted pyrrole;

forming a mercapto radical on the 2, 3 and/or 5 carbon atoms by alkaline hydrolysis and subsequent acidification of a 2-, 3- and/or 5-thiocyanopyrrole;

forming a mercapto radical on the 2, 3 and/or 5 carbon atoms by alkaline hydrolysis and subsequent acidification of an N-substituted 2-, 3- and/or 5-thiocyanopyrrole;

alkylation of the sulfur on the 2, 3 and/or 5 carbon atoms of a 2-, 3- and/or 5-thiocyanopyrrole to form an alkylthio radical;

alkylation of the sulfur on the 2, 3 and/or 5 carbon atoms of an N-substituted a 2-, 3- and/or 5-thiocyano-pyrrole to form an alkylthio radical;

oxidation of the sulfur on the 2, 3 and/or 5 carbon atoms of a 2-, 3- and/or 5-alkylthiopyrrole to form a corresponding 2-, 3- and/or 5-alkylsulfinylpyrrole;

oxidation of the sulfur on the 2, 3 and/or 5 carbon atoms of an N-substituted 2-, 3- and/or 5-alkylthio-pyrrole to form a corresponding N-substituted 2-, 3- and/or 5-alkylsulfinylpyrrole;

oxidation of the sulfur on the 2, 3 and/or 5 carbon atoms of a 2-, 3- and/or 5-alkylthiopyrrole to form a corresponding 2-, 3- and/or 5-alkylsulfonylpyrrole;

oxidation of the sulfur on the 2, 3 and/or 5 carbon atoms of an N-substituted 2-, 3- and/or 5-alkylthiopyrrole to form a corresponding N-substituted 2-, 3- and/or 5-alkylsulfonylpyrrole;

oxidation of the sulfur on the 2, 3 and/or 5 carbon atoms of a 2-, 3- and/or 5-alkylsulfinylpyrrole to form a corresponding 2-, 3- and/or 5-alkylsulfonylpyrrole;

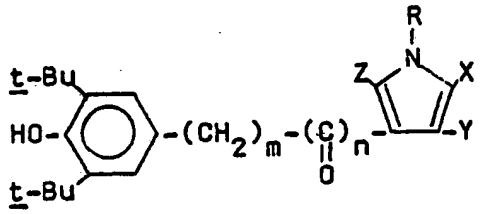
oxidation of the sulfur on the 2, 3 and/or 5 carbon atoms of an N-substituted 2-, 3- and/or 5-alkylsulfinylpyrrole to form a corresponding N-substituted 2-, 3- and/or 5-alkylsulfonylpyrrole;

reduction of a 3,5-di-t-butyl-4-hydroxyphenyl-oxoalkylpyrrole to the corresponding 3,5-di-t-butyl-4-hydroxyphenylalkylpyrrole;

addition of pharmaceutically acceptable bases to the compounds of Formula X'; and

release of salts to form the free compounds of Formula X'.

Another preferred process is a process for the preparation of compounds of formula X'



or a pharmaceutically acceptable salt thereof wherein:

m is an integer from zero to three;

n is an integer from zero to one;

m+n is an integer from one to three;

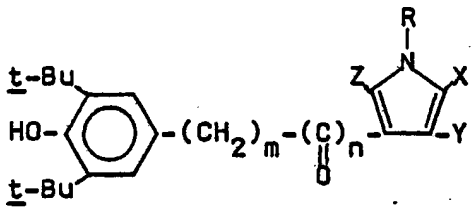
R is hydrogen, lower alkyl, carboxy lower alkylene, phenyl or benzyl; and

X, Y and Z are independently selected from hydrogen, lower alkyl, halo, SCN, SR', SOR", $SO_2R"$ and CF_3,

wherein R' is H, aryl, lower alkyl or lower alkanoyl; and R" is lower alkyl

which comprises

a) reacting a compound of the formula



(Formula X)

wherein:

"t-Bu-" refers to $-C(CH_3)_3$, the tertiary butyl radical;

m is an integer from zero to three;

n is an integer from zero to one;

m+n is an integer from one to three;

R is halo, or a removable directing group; and

X, Y and Z are independently selected from H, lower alkyl, CF_3, halo, SCN, SR', SOR" and $SO_2R"$ (wherein R' is H, aryl, lower alkyl or lower alkanoyl; and R" is lower alkyl or aryl)

with a strong base to form a compound of formula X' wherein R equals hydrogen; or

b) reacting a compound of formula X' wherein R equals hydrogen with the appropriate alkylating agent and an alkali metal hydride to form a compound of formula X' wherein R is lower alkyl, benzyl, phenyl, or carboxy lower alkylene; or

c) reacting a compound of formula X' wherein X, Y, and/or Z is/are hydrogen with thiocyanogen to form a compound of formula X' wherein X, Y, and/or Z is/are a thiocyano group; or

d) reacting a compound of formula X' wherein X, Y, and/or Z is/are a thiocyano group in an alcoholic solution of an inorganic base followed by acidification to form a compound of formula X' wherein X, Y, and/or Z is/are a mercapto group; or

e) reacting a compound of formula X' wherein X, Y, and/or Z is/are a thiocyano group with an alkali iodide followed by a methanolic solution of an inorganic base to form a compound of formula X' wherein X, Y, and/or Z is/are an alkylthio group; or

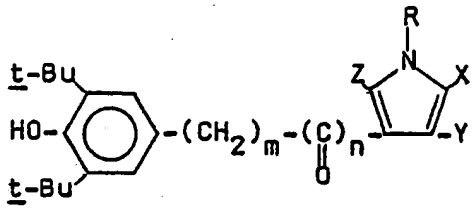
f) reacting a compound of formula X' wherein X, Y, and/or Z is/are a thiocyano group with an alkali metal acetate in an alkanoic acid and an alkanoic anhydride with a strong reducing agent to form a compound of formula X' wherein X, Y, and/or Z is/are a lower alkanoylthio group; or

g) oxidizing a compound of formula X' wherein X, Y, and/or Z is/are an alkylthio or alkylsulfinyl group to form a compound of formula X' wherein X, Y, and/or Z is/are an alkylsulfinyl or alkylsulfonyl group; or

h) reacting a compound of formula X' wherein X, Y, and/or Z is/are hydrogen with a halogenating agent to form a compound of formula X' wherein X, Y, and/or Z is/are halo; or

i) reacting a compound of formula X' wherein n is one with a strong reducing agent to form a compound of formula X' wherein n is zero; or

j) reacting a compound of the formula



or a pharmaceutically acceptable salt thereof wherein:

m is an integer from zero to three;
n is an integer from zero to one;
m+n is an integer from one to three;
R is halo; and
X, Y and Z are halo,

with a strong reducing agent to form a compound of formula X' wherein X, Y, and Z are halo; or

k) reacting a compound of formula X' wherein X and/or Y is/are chloro and Z is chloro with Zinc in acetic acid to form a compound of formula X' wherein Z is hydrogen; or

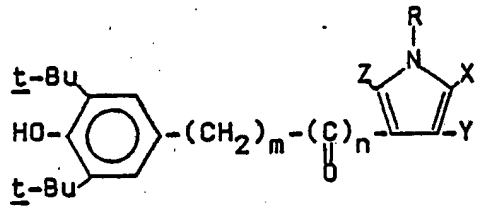
l) partitioning a mixture of compounds of formula X' wherein X is chloro and Y and/or Z is/are chloro between an aqueous base and a chlorinated solvent, to isolate a compound of formula X' wherein X is chloro and Y and Z are hydrogen in the resulting organic phase; or

m) converting a compound of formula X' to its pharmaceutically acceptable salt; or

n) converting a pharmaceutically acceptable salt of a compound of formula X' to the corresponding free compound of formula X'; or

o) converting a pharmaceutically acceptable salt of a compound of formula X' to another pharmaceutically acceptable salt of a compound of formula X'.

Another preferred process is a process for the preparation of a compound of formula X.



(Formula X)

or a pharmaceutically acceptable salt thereof wherein:

"t-Bu-" refers to $-C(CH_3)_3$, the tertiary butyl radical;

m is an integer from zero to two;

n is one;

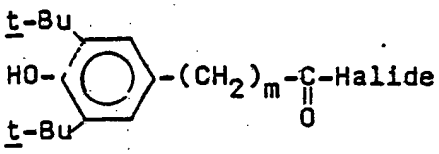
m+n is an integer from one to three;

R is halo, or a removable directing group; and

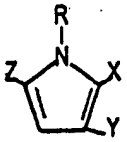
X, Y and Z are independently selected from H, lower alkyl, CF_3, halo, SCN, SR', SOR" and SO_2R" (wherein R' is H, aryl, lower alkyl or lower alkanoyl; and R" is lower alkyl or aryl)

which comprises

reacting a compound of the formula



wherein m is as defined above, with a compound of the formula



wherein R, X, Y, and Z are as defined above to form a compound of formula X.

Isolation and purification of the compounds and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography or thick-layer chromatography, or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be had by reference to the examples below. However, other equivalent separation or isolation procedures can, of course, also be used.

Utility, Testing and Administration

General Utility

The compounds of the present invention and the compositions containing them are useful as anti-inflammatory agents, analgetic agents, anti-pyretic agents, anti-psoriatic agents, anti-coronary occlusion agents (including anti-ischemia and anti-infarction) and as anti-bone degradative agents in mammals, whether human, domestic (cattle, pigs, sheep, goats, horses), or pets (cats, dogs); preferably in humans.

For example, compounds of Formula X' are useful for treating psoriasis or other allergic conditions such as conjunctivitis, bronchial asthma and inflammatory bronchial diseases, for treating inflammatory bowel disease, for treating arthritis (including rheumatoid arthritis, in which there is an immunologically driven inflammatory process), for treating pain, for treating

pyrexia, for lowering thromboxane levels and for treating bone degradative diseases.

Bone degradative (calcium loss) disorders against which the compounds of Formula X' are useful include, but are not limited to:

osteoporosis (whether senility-induced, post-menopausal, cirrhotic, bed-rest induced, and/or steroid-induced) [see Pacifici et al., Spontaneous release of interleukin 1 from human blood monocytes reflects bone formation in idiopathic osteoporosis, Proc. Natl. Acad. Sci., 84, 4616-4620 (1987)],

periodontitis (an alveolar bone resorptive disease) [see Williams et al., Flurbiprofen: A Potent Inhibitor of Alveolar Bone Resorption in Beagles, Science, 227, 640-642 (1985)], and

PTH mediated syndromes, such as, primary or secondary hyperparathyroidism, or PTH-like factor mediated syndromes, such as, tumor-related hypercalcemia including humoral-induced hypercalcemia of malignancy [see Barnes, New Tumor Factor May Disrupt Calcium Levels, Science, 237, 363-364 (1987)].

The compounds of the present invention and the compositions containing them are also useful against metabolic bone disorders in mammals (as defined above) and in avians (such as chickens); preferably in humans. Metabolic bone disorders against which the compounds of Formula X' are useful include, but are not limited to osteopetrosis and Paget's Disease (which often coexists with hyperparathyroidism).

Testing

Anti-inflammatory activity is determined by following tests: the Adjuvant-Induced Arthritis Assay [Pearson, Proc. Soc. Exp. Biol. Med., 91: 95-101 (1956)]; the Carrageenan-Induced Rat Paw Inflammation Assay

[Winter, et al., Proc. Soc. Exp. Biol. Med., 111: 544-547 (1962)]; the Arachidonic Acid-Induced Mouse Ear Edema Assay [Young, et al., J. Invest. Derm., 82: 367-371 (1984)]; the Phenylquinone-induced Mouse Writhing Assay [Hendershot, et al., J. Pharmacol. Exp. Ther., 125: 237-240 (1959)]; and the Human Polymorphonuclear Leukocyte (HPMN) Assay [Radmark, et al., Febs Letters, 110(2): 213-215 (1980)].

The anti-inflammatory effectiveness of 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (Formula XI) was compared with that of 2-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (Formula I) by conducting the above-described assays. These assays and their results are reported in Examples 30-35 and 37. The results show that the representative compound of the present invention has demonstrated increased anti-inflammatory potency over the closest known anti-inflammatory agent. The other compounds according to Formula X' also have the desired activities. All of the compounds of the present invention are quite specific as to cyclooxygenase, lipoxygenase and/or superoxide radical anion inhibition, and/or thromboxane lowering activity and are very well tolerated, e.g., having a high LD_{50}, low ulcerogenicity and the like.

Thromboxane levels are measured by RIA, according to established procedures; RIA kits for thromboxane (TXB_2) are commercially available from New England Nuclear.

Antipyretic activity is measured, for example, by the Test for Antipyretic Activity Using Yease-induced Fever in the Rat, as described, e.g., by Roszkowski, A.P. et al. [Anti-inflammatory and Analgesic Properties of d-2-(6'-methoxy-2'-naphthyl)propionic acid (naproxen), J. Pharmacol. Exp. Ther., 179, 114 (1971).

Anti-bone-degradative activity is determined by both in vitro and in vivo methods. In each instance, a

mediator known to cause bone resorption is administered to a test system, adding a control (placebo or a known active compound, e.g., flurbiprofen) or a test compound, and measuring differences in free calcium ion as an indicator of bone degradative inhibition.

In vitro bone resorption inhibition testing methods using parathyroid hormone ("PTH", typically obtained from the bovine, or "bPTH") to induce bone loss have been described by Raisz and Niemann [Effect of Phosphate, Calcium and Magnesium on Bone Resorption and Hormonal Responses in Tissue Culture, Endocrinology, 85, 446-452 (1969)], by Raisz et al. [Effects of Thionapthene 2-Carboxylic Acid and Related Compounds on Bone Resorption in Organic Culture, Calcif. Tissue Int., 37, 556-559 (1985)], and in the published European Patent Application of Takeda Chemical Industries, Ltd. EP 0 146 921 [see particularly Test Example I at pages 9-10, where the method of Raisz from J. Clin. Invest., 44, 103-116 (1965) is described].

In vitro bone resorption inhibition testing methods using Interleukin ("IL-1β") to induce bone loss have been described by Gowen and Mundy [Actions of Recombinant Interleukin 1, Interleukin 2, and Interferon-γ on Bone Resorption In Vitro, J. Immunol., 136(7), 2478-2482 (1986)], by Chin et al. [Human Interleukin IL-1β, A More Powerful Inducer of Bone Demineralization Than IL-1-α, PTH or PGE_2 In Vitro, Fed. Proc., 45, 454 (1986)], and as recently described by Stashenko et al. [Synergistic Interactions Between Interleukin 1, Tumor Necrosis Factor, and Lymphotoxin in Bone Resorption, J. Immunol., 138(5), 1464-1468 (1987)].

The effectiveness of the compounds of Formula X' against bone disorders was tested by conducting in vitro assays such as those described above. These assays and their results are reported in Examples 39 and 40. The

results show that the representative compounds of the present invention have demonstrated utility for treating bone disorders, with equal or greater potency than the compounds presently used for such treatment.

In vivo methodology involves inducing a bone calcium loss response by osmotic pump introduction of bPTH or IL-1β to test animals, followed by administration of test compound or controls, measuring serum free calcium ion level differences as indicative of bone resorption inhibition. Also see, for example, Johannesson et al. [Thionapthene-2-Carboxylic Acid: A New Antihypercalcemic Agent, Endocrinology, 117(4) 1508-1511 (1985)] and Jeffcoat et al. [Flurbiprofen treatment of periodontal disease in beagles, J. Periodontal Res., 21, 624-633 (1986)].

Administration and Formulation.

Dose

One aspect of the present invention relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula X', and/or a pharmaceutically accepted salt thereof, in admixture with a pharmaceutically acceptable non-toxic carrier. A therapeutically effective amount (i.e., a dosage sufficient to provide treatment for the disease state being treated, e.g., inflammation, pain, pyrexia, ischemic heart disease and/or bone disorders) of the compounds of the present invention may range between about 0.1 µg/kg to about 50.0 mg/kg of body weight per day, depending on the animal and disease state being treated, and on the method of administration (e.g., systemic vs. topical).

Higher concentrations (preferably in the range of about 1.0 to 25.0 mg/kg, optimally, about 15.0 mg/kg) are expected to be used for systemic treatment of inflammation, pain, pyrexia and psoriasis.

Lower concentrations (preferably in the range of about 1 µg/kg to about 400 µg/kg; optimally about 300 µg/kg for a human, and optimally about 1 µg/kg in the dog or chicken) are expected to be used for systemic treatment of bone degradative and metabolic bone growth disorders.

Formulations

The level of the drug in a formulation can vary within the full range employed by those skilled in the art, e.g., from about .01 percent weight (%w) to about 99.99%w of the drug based on the total formulation and about 0.01%w to 99.99%w excipient. Preferably the drug is present at a level of about 10%w to about 70%w.

Useful pharmaceutical carriers for the preparation of the pharmaceutical compositions hereof can be solids or liquids. Thus, the compositions can take the form of tablets, pills, capsules, powders, sustained release formulations, solutions, suspensions, gels, pastes, elixirs, aerosols, and the like. Carriers can be selected from the various oils, including those of petroleum, animal, vegetable or synthetic origin, for example, peanut oil, soybean oil, mineral oil, sesame oil, and the like. Water, saline, aqueous dextrose, and glycols are preferred liquid carriers, particularly for injectable solutions. Suitable solid pharmaceutical carriers include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, glycerol, propylene glycol, water, ethanol, and the like. Other suitable pharmaceutical carriers and their formulations are described in "Remington's Pharmaceutical Sciences" by E. W. Martin.

Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies) are also

preferred as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811 (the pertinent portions of which are incorporated herein by reference). For example, liposome formulations may be prepared by dissolving appropriate lipid(s) (such as stearoyl phosphatidyl ethanolamine, stearoyl phosphatidyl choline, arachadoyl phosphatidyl choline, and cholesterol) in an inorganic solvent that is then evaporated, leaving behind a thin film of dried lipid on the surface of the container. An aqueous solution of the active compound [e.g., 2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, 2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, or 2-chloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole] is then introduced into the container. The container is then swirled by hand to free lipid material from the sides of the container and to disperse lipid aggregates, thereby forming the liposomal suspension.

Administration

Another aspect of the present invention relates to a method for treating inflammatory diseases such as arthritis, pain, pyrexia, psoriasis, conjunctivitis, bronchial asthma, inflammatory bronchial diseases, ischemic heart disease, inflammatory bowel diseases, bone degradative diseases, and/or metabolic bone growth disorders, which method comprises administering a therapeutically effective amount of a compound of Formula X' to an animal in need thereof.

In the practice of the above-described method of the present invention, a therapeutically effective amount of the compound of Formula X' or a pharmaceutical composition containing same is administered via any of the usual and acceptable methods known in the art, either singly or in combination with another compound or

compounds of the present invention or other pharmaceutical agents. The formulations can be administered in a single unit dosage form for continuous treatment or in a single unit dosage form ad libitum when relief of symptoms is specifically required.

These compounds or compositions can be administered systemically (e.g., orally, transdermally, intranasally or by suppository), parenterally (e.g., intramuscularly, subcutaneously and intravenously), or topically (e.g., by dermal application of an ointment, gel or salve, and by oral application in a chewing gum, toothpaste, oral gel or rinse). They can be administered either in the form of solid, semi-solid or liquid dosages including tablets, solutions, suspensions, gels, pastes, aerosols, and the like, as discussed in more detail above. It is preferred to administer compounds of Formula X' systemically via the oral route, except in the treatment of periodontitis where both oral systemic and topical administration are preferred.

EXAMPLES

The following examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as a limitation on the scope of the invention, but merely as being illustrative and representative thereof.

EXAMPLE 1
Synthesis of N-phenylsulfonyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole

1A. Formula X Where R is Phenylsulfonyl

6.65 G of 3,5-di-t-butyl-4-hydroxybenzoic acid was converted into its acid chloride by suspending it in 20 ml of dry methylene chloride and reacting it with 4 g of thionyl chloride followed by 7 drops of DMF. After 20 minutes, a sample treated with methanol showed no remaining acid. The solution was evaporated to dryness, and then azeotropically distilled twice with benzene, to remove excess thionyl chloride.

The crude acid chloride was dissolved in dichloroethane (125 ml), and $AlCl_3$ (3.85 g) was added. The mixture was stirred for 10 minutes at room temperature. N-phenylsulfonylpyrrole (5.0 g) dissolved in dichloroethane (50 ml) was added. The reaction mixture was stirred at room temperature for 90 minutes, poured into a 50:50 water-methylene chloride mixture and stirred. The layers were separated and the organic solution was dried on sodium sulfate. After evaporation of the solvent to dryness, the residue was recrystallized from methanol to give 6.50 g of a white crystalline powder, identified as N-phenylsulfonyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, the compound of Formula XII (and a compound according to Formula X wherein: m is 0; n is 1; R is $SO_2\phi$; and X, Y and Z are H) (mp 214-215.5°C - corrected).

Analysis calculated for $C_{25}H_{29}NO_4S$ (mw 439.556):

Theoretical: C, 68.31; H, 6.65; N, 3.19;

Found: C, 68.34; H, 6.89; N, 3.04.

1B. Formula X Where R is Phenylsulfonyl and X, Y and/or Z are Halo or Lower Alkyl

Similarly, by following the procedure of part A above and substituting for N-phenylsulfonylpyrrole the following starting materials:

N-phenylsulfonyl-3-chloropyrrole,
N-phenylsulfonyl-2-(trifluoromethyl)pyrrole,
N-phenylsulfonyl-2,5-di-methylpyrrole, and
N-phenylsulfonyl-2-ethylpyrrole;

there are obtained the following respective compounds:

N-phenylsulfonyl-3-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-phenylsulfonyl-2-(trifluoromethyl)-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-phenylsulfonyl-2,5-dimethyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and

N-phenylsulfonyl-2-ethyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole.

1C. Formula X Where R is a Removable Directing Group Other Than Phenylsulfonyl

Similarly, by following the procedure of part A above and substituting for N-phenylsulfonylpyrrole the following starting materials:

N-p-tolylsulfonylpyrrole,
N-methylsulfonyl-2,5-dimethylpyrrole, and
N-benzylsulfonylpyrrole;

there are obtained the following respective compounds:

N-p-tolylsulfonyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole [(recrys. from methanol, mp 121-123°C); ^{1}H nmr: 1.48s (18H), 2.43s (3H), 5.73s (OH), 6.8m (1H), 7.25m (1H), 7.38s (1H), 7.76m (6H)],

N-methylsulfonyl-2,5-dimethyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and

N-benzylsulfonyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole.

1D. Formula X Where R is Phenylsulfonyl, m is 1-2 and n is 1

Similarly, by following the procedure of part A above and substituting for 3,5-di-t-butyl-4-hydroxybenzoic acid the following starting materials:

3,5-di-t-butyl-4-hydroxyphenylacetic acid, and

3-(3,5-di-t-butyl-4-hydroxyphenyl)propanoic acid;

there are obtained the following respective compounds:

N-phenylsulfonyl-3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole, and

N-phenylsulfonyl-3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]pyrrole.

EXAMPLE 2
Synthesis of
3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole

2A. Formula XI

3 G of N-phenylsulfonyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, a material obtained in Example I, was dissolved in dioxane (300 ml) and methanol (100 ml), and 5N sodium hydroxide (100 ml) was added. The solution was heated on steam for 20 minutes, concentrated under reduced pressure and partitioned between ether and water. The ether layer was washed once with water, dried on sodium sulfate and evaporated to dryness.

The crude solid thus obtained was taken up in methylene chloride and passed through a short alumina column (3% H_2O). The first yellow fraction was discarded, after which the desired product, 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, the compound of Formula XI (and a compound according to Formula X wherein: m is 0; n is 1; R is H; and X, Y and Z are H), came off. The solid so obtained was homogeneous on the tlc and weighed 2.0 g; it was recrystallized from ether-hexane (mp 170.5-171.0°C - corrected).

Analysis calculated for $C_{19}H_{25}NO_2$ (mw 299.398):

Theoretical:	C, 76.22; H, 8.42; N, 4.68;
Found:	C, 76.41; H, 8.66; N, 4.63.

2B. Formula X Where X, Y and/or Z are Halo or Lower Alkyl

Similarly, by following the procedure of part A above and substituting for N-phenylsulfonyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

N-phenylsulfonyl-3-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-phenylsulfonyl-2-(trifluoromethyl)-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-phenylsulfonyl-2,5-dimethyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and

N-phenylsulfonyl-2-ethyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole;

there are obtained the following respective compounds:

3-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

2-(trifluoromethyl)-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

2,5-dimethyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole, and

2-ethyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole.

2C. Formula X Where R is a Removable Directing Group Other Than Phenylsulfonyl

Similarly, by following the procedure of part A above and substituting for N-phenylsulfonyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

N-p-tolylsulfonyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-methylsulfonyl-2,5-dimethyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and

N-benzylsulfonyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole;

there are obtained the following respective compounds:

3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

2,5-dimethyl-3-(3,5-di-t-butyl4-hydroxybenzoyl) pyrrole, and

3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole.

2D. Formula X Where m is 1-2 and n is 1

Similarly, by following the procedure of part A above and substituting for N-phenylsulfonyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

N-phenylsulfonyl-3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole, and

N-phenylsulfonyl-3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]pyrrole;

there are obtained the following respective compounds:

3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]-pyrrole, and

3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]-pyrrole.

EXAMPLE 3
Synthesis of
N-methyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole

3A. Formula X Where R is Methyl

2 G (6.6 mmol) of 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole were added to a stirred suspension of 640 mg (13 mmol) of sodium hydride (50% in mineral oil) in 20 ml of anhydrous dimethylformamide. After 1 hour at room temperature, 0.415 ml (6.68 mmol) of methyl iodide was added, and stirring at room temperature was continued for an additional hour. Nitrogen was then bubbled

through the reaction mixture for 10 minutes and thereafter the reaction mixture was partitioned between methylene chloride and water. The organic phase was washed with water, dried and evaporated in vacuo. Purification of the crude product by t.l.c. using hexane:ethyl acetate (80:20) afforded 1.439 g (69%) of the title compound, which was recrystallized from methylene chloride-hexane (mp 135.5-136.5°C).

3B. Formula X Where R is Carboxy Lower Alkylene, Benzyl or Lower Alkyl Other Than Methyl

Similarly, by following the procedure of part A above and substituting for methyl iodide the following starting materials:

bromoacetic acid (with an additional molar equivalent of NaH),
ethyl iodide,
propyl bromide,
butyl chloride, and
benzyl bromide;

there are obtained the following respective compounds:

3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole-N-acetic acid,
N-ethyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (mp 73-75°C),
N-propyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-butyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (mp 101-103°C), and
N-benzyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (mp 123-124°C).

3C. Formula X Where R is Methyl, m is 1-3 and n is 0-1

Similarly, by following the procedure of part A above and substituting for 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,
3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]pyrrole,
3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]-pyrrole, and
3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]-pyrrole,
there are obtained the following respective compounds:
N-methyl-3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,
N-methyl-3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]-pyrrole,
N-methyl-3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxo-ethyl]pyrrole, and
N-methyl-3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxo-propyl]pyrrole.

30. Formula X Where R is Other Than Methyl, m is 1-3 and n is 0-1

Similarly, by following the procedure of part A above and substituting for 3-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole the following starting materials:
3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole, and
3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]-pyrrole,
and substituting for methyl iodide the following starting materials:
ethyl iodide, and
benzyl bromide;
there are obtained the following compounds:
N-ethyl-3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,
N-benzyl-3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,
N-ethyl-3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxo-ethyl]pyrrole, and
N-benzyl-3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxo-ethyl]pyrrole.

3E. Formula X Where R is Methyl and X, Y and/or Z is Lower Alkyl or Halo

Similarly, by following the procedure of part A above and substituting for 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

2,5-dimethyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole,

3-ethyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

2-(trifluoromethyl)-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and

2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole;

there are obtained the following compounds:

N-methyl-2,5-dimethyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-methyl-3-ethyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole,

N-methyl-2-(trifluoromethyl)-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and

N-methyl-2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole.

EXAMPLE 4
Synthesis of
N-ethyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole

4A. Formula X Where R is Ethyl

2 G (6.6 mmol) of 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole were added to a cooled, stirred suspension of 0.70 g of sodium hydride (50% in mineral oil) in 50 ml of anhydrous dimethylformamide under nitrogen. After 30 minutes at room temperature, 0.7 ml of ethyl iodide was added, and stirring at room temperature was continued for an additional 2 hours. The reaction mixture was poured over a 10% HCl - ice mixture, then extracted three times with 250 ml ethyl acetate.

The organic layer was washed five times with 200 ml water, dried and evaporated to dryness. The residue was purified by chromatography on alumina (3% water, 100 g) eluting with hexane:ethyl acetate (9:1). Crystallization from methylene chloride-hexane gave 1.11 g of N-ethyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (mp 73-75°C). ^1H nmr: 1.5m (21H), 3.93c (2H), 5.56s (OH), 6.63m (2H), 7.25m (1H), 7.80s (2H).

Anal. Calcd. for $C_{21}H_{29}NO_2$ (mw 333.94):

Theoretical:	C, 75.52; H, 8.90; N, 4.19;
Found:	C, 75.83; H, 8.95; N, 4.12.

4B. Formula X Where R is Propyl

Similarly, by following the procedure of part A above and substituting propyl iodide for ethyl iodide, there is obtained N-propyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole.

EXAMPLE 5

Synthesis of N-n-butyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole

5A. Formula X Where R is n-Butyl

2 G (6.6 mmol) of 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole were added to a cooled, stirred suspension of 0.69 g of sodium hydride (50% in mineral oil) in 50 ml of anhydrous dimethylformamide under nitrogen. After 1 hour at 20°C, 0.8 ml of n-butyl bromide was added. Stirring was continued for an additional 18 hours at room temperature. The reaction mixture was poured over a 10% HCl-ice mixture, then extracted three times with 250 ml ethyl acetate. The organic layer was washed five times with 200 ml water, dried and evaporated to dryness. The residue was purified on a silica column (200 g) eluting with

hexane:ethyl acetate (9:1). Crystallization from acetone-hexane gave 1.52 g of N-n-butyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (mp 101-103°C).
^{1}H nmr: 0.9t (3H), 1.5s (18H), 1.63m (4H), 3.9t (2H), 5.6s (OH), 6.68d (1H), 7.26m (1H), 7.86s (2H).
Anal. Calcd. for $C_{23}H_{33}ON$ (mw 355.49):

Theoretical:	C, 77.70; H, 9.35; N, 3.94;
Found:	C, 77.55; H, 9.52; N, 3.80.

5B. Formula X Where R is Lower Alkyl Other Than n-Butyl

Similarly, by following the procedure of part A above and substituting for n-butyl bromide the following starting materials:

s-butyl bromide, and
i-propyl bromide;

there are obtained the following respective compounds:

N-s-butyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and
N-i-propyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole.

EXAMPLE 6
Synthesis of
N-benzyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole

6A. Formula X Where R is Benzyl

2 G (6.6 mmol) of 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole were added to a cooled, stirred suspension of 0.70 g of sodium hydride (50% in mineral oil) in 50 ml of anhydrous dimethylformamide under nitrogen. After 30 minutes at room temperature, 1.0 ml of benzyl bromide was added. Stirring at room temperature was continued for an additional 16 hours. The reaction mixture was poured over a 10% HCl-ice mixture, then extracted three times with 250 ml ethyl acetate. The organic layer was washed five times with

200 ml water, dried and evaporated to dryness. The residue was purified by chromatography on alumina (3% water, 100 g) eluting with hexane:ethyl acetate (9:1). Crystallization from methylene chloride-hexane gave 1.5 g of N-benzyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (mp 123-124°C).

^{1}H nmr: 1.45s (18H), 5.06s (2H), 5.56s (OH), 6.73m (2H), 7.31m (6H), 7.76s (2H).

Anal. Calcd. for $C_{26}H_{31}O_2N$ (mw 389.51):

Theoretical:	C, 80.16; H, 8.02; N, 3.59;
Found:	C, 80.17; H, 8.17; N, 3.47.

EXAMPLE 7

Synthesis of N-methyl-2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole

7A. Formula X Where R is Methyl and X, Y and Z are Cl

2,4,5-Trichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole (3.3 g) dissolved in DMF (35 ml) was treated with sodium hydride (50%, .432 g) in 4 portions, under nitrogen with stirring at room temperature. After 1 hour at room temperature, 0.56 ml of methyl iodide was added, dropwise, via microsyringe. After stirring 5 minutes more, the reaction mixture was poured into water (300 ml). The organic layer was separated, dried and evaporated to dryness. The residue was purified on silica gel, eluting with hexane:ethyl acetate (80:20). The pure product was recrystallized from ether-pentane to give 2.73 g of the title compound (mp 155-156°C).

7B. Formula X Where R is Other Than Methyl

Similarly, by following the procedure of part A above and substituting for methyl iodide the following starting materials:

bromoacetic acid (with an additional molar equivalent of NaH),
benzyl bromide,
s-butyl bromide, and
n-propyl bromide;
there are obtained the following respective compounds:
2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole-N-acetic acid,
N-benzyl-2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-s-butyl-2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and
N-n-propyl-2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole.

7C. Formula X Where X, Y and/or Z is Halo Other Than Trichloro

Similarly, by following the procedure of part A above and substituting for 2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:
2,5-dichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole,
2,4,5-tribromo-3-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole, and
2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole;
there are obtained the following respective compounds:
N-methyl-2,5-dichloro-3-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole,
N-methyl-2,4,5-tribromo-3-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole, and
N-methyl-2-chloro-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole.

7D. Formula X Where R is Other Than Methyl and X is Halo Other Than Trichloro

Similarly, by following the procedure of part C above and substituting for methyl iodide the following starting materials:

benzyl bromide,
s-butyl bromide, and
n-propyl bromide;

there are obtained the following respective compounds:

N-benzyl-2,5-dichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-benzyl-2,4,5-tribromo-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-benzyl-2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-s-butyl-2,5-dichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-s-butyl-2,4,5-tribromo-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-s-butyl-2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-n-propyl-2,5-dichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-n-propyl-2,4,5-tribromo-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and

N-n-propyl-2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole.

7E. Formula X Where m is 1 and n is 0

Similarly, by following the procedure of part A above and substituting 2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole for 2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, there is obtained N-methyl-2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole.

EXAMPLE 8
Synthesis of N-methyl-2-methylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole

8A. Formula X Where R is Methyl and X is SR'

2-Methylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole (1 g) was added to a cooled, stirred suspension of 0.28 g of sodium hydride (50% in mineral oil) in 20 ml of anhydrous dimethylformamide under nitrogen. After 45 minutes at room temperature, the mixture was cooled to 0°C and 0.25 ml of methyl iodide was added. After 30 minutes, the reaction mixture was poured into a 10% HCl-ice-water mixture, then extracted three times with 100 ml ethyl acetate. The organic layer was washed five times with 100 ml water, dried and evaporated to dryness. Crystallization of the residue from ethyl acetate-hexane gave 0.93 g of the title compound (mp 173-175°C).

8B. Formula X Where R is Other Than Methyl

Similarly, by following the procedure of part A above and substituting for methyl iodide the following starting materials:

bromoacetic acid (with an additional molar equivalent of NaH),

benzyl bromide,

s-butyl bromide, and

n-propyl bromide;

there are obtained the following respective compounds:

2-methylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole-N-acetic acid,

N-benzyl-2-methylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-s-butyl-2-methylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and

N-n-propyl-2-methylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole.

8C. Formula X Where X is a Sulfur-based Radical Other Than 2-Methylthio

Similarly, by following the procedure of part A above and substituting for 2-methylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

3-methylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole,

2,3-dimethylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole,

2-ethylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole,

3-(3,5-di-t-butyl-4-hydroxybenzoyl)-5-thiocyano-pyrrole,

2,3-dithiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole,

2-methylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole,

2,5-dimethylsulfinyl-3-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole, and

3-methylsulfonyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole;

there are obtained the following respective compounds:

N-methyl-3-methylthio-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole,

N-methyl-2,3-dimethylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-methyl-2-ethylthio-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole,

N-methyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)-5-thiocyanopyrrole,

N-methyl-2,3-dithiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-methyl-2-methylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-methyl-2,5-dimethylsulfinyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and

N-methyl-3-methylsulfonyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole.

8D. Formula X Where X is a Sulfur-based Radical Other Than 2-Methylthio and R is Other Than Methyl

Similarly, by following the procedure of part A above and substituting for 2-methylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

2-ethylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole,

3-thiocyano-4-[2-(3,5-di-t-butyl-4-hydroxybenzoyl)-1-oxoethyl]pyrrole, and

2-methylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole,

and substituting for methyl iodide the following starting materials:

ethyl iodide, and

benzyl bromide;

there may be obtained the following compounds:

N-ethyl-2-ethylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-ethyl-3-[2-(3,5-di-t-butyl-4-hydroxybenzoyl)-1-oxoethyl]-4-thiocyanopyrrole,

N-ethyl-2-methylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-benzyl-2-ethylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-benzyl-3-[2-(3,5-di-t-butyl-4-hydroxybenzoyl)-1-oxoethyl]-4-thiocyanopyrrole, and

N-benzyl-2-methylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole.

8E. Formula X Where m is 1-3 and n is 0-1

Similarly, by following the procedure of part A above and substituting for 2-methylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

2-methylthio-4-(3,5-di-t-butyl-4-hydroxybenzyl)-pyrrole, and

2-methylthio-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole,

there may be obtained the following compounds:

N-methyl-2-methylthio-4-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole, and

N-methyl-2-methylthio-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole.

EXAMPLE 9

Synthesis of 2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole and 2,3-di-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole

9A. Formula X Where X and/or Y is Cl

A stirred solution of 2 g (6.68 mmol) of 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole in 25 ml of anhydrous methylene chloride was treated dropwise, at room temperature, with 0.26 ml (450 mg, 3.34 mmol) of sulfuryl chloride. The resulting mixture was stirred for 30 minutes and then poured into saturated sodium bicarbonate solution. The organic phase was separated and the aqueous phase extracted with methylene chloride. The combined organic extract was dried and evaporated

under vacuo. The residue was purified by repeated tlc, using hexane-ethyl acetate (80:20) for the first development, thus obtaining 413 mg of recovered starting material plus 1.144 g of a mixture of more polar products.

This mixture was separated by tlc using methylene chloride (2 developments), and recrystallized from ethyl acetate-hexane, to afford:

(a) 462 mg (20.7%) of 2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, a compound according to Formula X wherein: m is 0; n is 1; R is H; X is Cl; and Y and Z are both H (mp 222-223°C);

Anal. Calcd. for $C_{19}H_{24}ClNO_2$ (mw 333.84):

Theoretical:	C, 68.35; H, 7.24; N, 4.19;
Found:	C, 68.60; H, 7.14; N, 4.13;

and (b) 604 mg (24.5%) of 2,3-dichloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, a compound according to Formula X wherein: m is 0; n is 1; R is H; X and Y are each Cl; and Z is H (mp 258-259°C - uncorrected);

Anal. Calcd. for $C_{19}H_{23}Cl_2NO_2$ (mw 368.287):

Theoretical:	C, 61.95; H, 6.29; N, 3.80;
Found:	C, 61.97; H, 6.21; N, 3.70.

98. Formula X Where X and/or Y is Cl and R is Lower Alkyl or Benzyl

Similarly, by following the procedure of part A above and substituting for 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

N-methyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-ethyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-i-propyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-butyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
and
N-benzyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

there are obtained the following respective compounds:

N-methyl-2-chloro-4-(3,5-di-t-butyl-4-hydroxbenzoyl)-pyrrole,

N-methyl-2,3-dichloro-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole,

N-ethyl-2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole,

N-ethyl-2,3-dichloro-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole,

N-i-propyl-2-chloro-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole,

N-i-propyl-2,3-dichloro-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole,

N-butyl-2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole,

N-butyl-2,3-dichloro-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole,

N-benzyl-2-chloro-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole, and

N-benzyl-2,3-dichloro-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole.

9C. Formula X Where X and/or Y is Cl, m is 1-3 and n is 0-1

Similarly, by following the procedure of part A above and substituting for 3-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole the following starting materials:

3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,

3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]pyrrole,

3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]-pyrrole, and

3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]-pyrrole,

there may be obtained the following respective compounds:

2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,

2,3-dichloro-4-(3,5-di-t-butyl-4-hydroxybenzyl)-pyrrole,

2-chloro-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-propyl]pyrrole,

2,3-dichloro-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-propyl]pyrrole,

2-chloro-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxo-ethyl]pyrrole,

2,3-dichloro-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole

2-chloro-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxo-propyl]pyrrole, and

2,3-dichloro-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]pyrrole.

9D. Formula X Where X and/or Y is Cl, R is Other Than Methyl, m is 1-3 and n is 0-1

Similarly, by following the procedure of part A above and substituting for 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

N-benzyl-3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole, and

N-ethyl-3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxo-ethyl]pyrrole;

there may be obtained the following compounds:

N-benzyl-2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzyl)-pyrrole,

N-benzyl-2,3-dichloro-4-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,

N-ethyl-2-chloro-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole, and

N-ethyl-2,3-dichloro-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole.

EXAMPLE 10
Synthesis of
2,5-dichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole
and
2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole

10A. Formula X Where X and Z, or X, Y and Z are Chloro

A solution of 4 g. (13.3 mmol) of 3(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole in 30 ml of anhydrous methylene chloride was treated dropwise at room temperature and under stirring with 1.8 g (1.068 ml, 13.3 mmoles) of sulfuryl chloride. After 30 minutes, 1.068 ml more of this reagent was added. the mixture was stirred for 30 minutes further, and thereafter poured into saturated sodium bicarbonate solution. The organic layer was separated and the aqueous layer extracted with methylene chloride. The combined extracts were dried and the solvent eliminated under reduced pressure. The residue was purified by a combination of tlc (silica gel) and column chromatography (deactivated alumina, 3% water) to afford:

711 mg (14.5%) of 2,5-dichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, a compound according to Formula X wherein: m is 0; n is 1; R is H; Y is H; and X and Z are both Cl (mp 202-203°C),

analysis calculated for $C_{19}H_{23}Cl_2NO_2$ (mw 368.287):

Theoretical:	C, 61.95; H, 6.29; N, 3.80
Found:	C, 62.19; H, 6.07; N, 3.78;

and

990 mg (18.5%) of 2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, a compound according to Formula X wherein: m is 0; n is 1; R is H; and X, Y and Z are each Cl (mp 212-213°C),

analysis calculated for $C_{19}H_{22}Cl_3NO_2$ (mw 402.747):

Theoretical:	C, 56.65; H, 5.50; N, 3.47
Found:	C, 56.65; H, 5.49; N, 3.43.

108. Formula X Where X and Z, or X, Y and Z are Chloro and R is Lower Alkyl or Benzyl

Similarly, by following the procedure of part A above and substituting for 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

N-methyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-ethyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-i-propyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-butyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
and
N-benzyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

there are obtained the following respective compounds:

N-methyl-2,5-dichloro-4-(3,5-di-t-butyl-4-hydroxbenzoyl)pyrrole,
N-methyl-2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-ethyl-2,5-dichloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-ethyl-2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-i-propyl-2,5-dichloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-i-propyl-2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-butyl-2,5-dichloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-butyl-2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-benzyl-2,5-dichloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and
N-benzyl-2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole.

10C. Formula X Where X and Z, or X, Y and Z are Chloro, m is 1-3 and n is 0-1

Similarly, by following the procedure of part A above and substituting for 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,

3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]pyrrole,

3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]-pyrrole, and

3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]-pyrrole,

there may be obtained the following respective compounds:

2,5-dichloro-4-(3,5-di-t-butyl-4-hydroxybenzyl)-pyrrole,

2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzyl)-pyrrole,

2,5-dichloro-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-propyl]pyrrole,

2,4,5-trichloro-3-[3-(3,5-di-t-butyl-4-hydroxy-phenyl)propyl]pyrrole,

2,5-dichloro-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole,

2,4,5-trichloro-3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole,

2,5-dichloro-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]pyrrole, and

2,4,5-trichloro-3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]pyrrole.

10D. Formula X Where X and Z, or X, Y and Z are Chloro, R is Other Than Methyl, m is 1-3 and n is 0-1

Similarly, by following the procedure of part A above and substituting for 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

N-benzyl-3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole, and

N-ethyl-3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole;

there may be obtained the following compounds:

N-benzyl-2,5-dichloro-4-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,

N-benzyl-2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,

N-ethyl-2,5-dichloro-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole, and

N-ethyl-2,4,5-trichloro-3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole.

EXAMPLE 11
Synthesis of
2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole

11A. Formula X Where X is Chloro

1.0 G (.003 mole) of 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole was dissolved in 40 ml of methylene chloride and 10 ml of acetone, and cooled to 0°C. The cooled solution was stirred and to it was added 0.585 g (0.0029 mole) of 1,3-dichloro-5,5-dimethylhydantoin. Stirring was continued for 90 minutes at 0°C. The reaction mixture was washed with water. The organic phase was dried over sodium sulfate and the solvent was removed *in vacuo*. The residue was purified by tlc (silica gel) using hexane:ethyl acetate (3:1) as the developing solvent, followed by recrystallization to yield 43% of the title compound, 2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (having the same analytical characteristics for the compound as made in Example 9A).

11B. Formula X Where X is Cl and R is Lower Alkyl or Benzyl

Similarly, by following the procedure of part A above and substituting for 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

N-methyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-ethyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-i-propyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-butyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
and
N-benzyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

there are obtained the following respective compounds:

N-methyl-2-chloro-4-(3,5-di-t-butyl-4-hydroxbenzoyl)-pyrrole,
N-ethyl-2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole,
N-i-propyl-2-chloro-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole,
N-butyl-2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole, and
N-benzyl-2-chloro-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole.

11C. Formula X Where X is Cl, m is 1-3 and n is 0-1

Similarly, by following the procedure of part A above and substituting for 3-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole the following starting materials:

3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,
3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]pyrrole,
3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]-pyrrole, and
3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]-pyrrole,

there may be obtained the following respective compounds:

2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,

2-chloro-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-propyl]pyrrole,

2-chloro-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxo-ethyl]pyrrole, and

2-chloro-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxo-propyl]pyrrole.

11D. Formula X Where X is Cl, R is Other Than Methyl, m is 1-3 and n is 0-1

Similarly, by following the procedure of part A above and substituting for 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

N-benzyl-3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole, and

N-ethyl-3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxo-ethyl]pyrrole;

there may be obtained the following compounds:

N-benzyl-2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzyl)-pyrrole, and

N-ethyl-2-chloro-4-[2-(3,5-di-t-butyl-4-hydroxy-phenyl)-1-oxoethyl]pyrrole.

EXAMPLE 12
Synthesis of 1,2,4,5-tetrachloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole

12A. Formula X Where R, X, Y and Z are Chloro

50.0 G (.167 mole) of 3-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole was suspended in 500 ml of methylene chloride and cooled to -70°C with stirring. To this was added, all at once, 60 ml (0.746 mole) of sulfuryl chloride. The cooling bath was removed and the reaction temperature slowly rose to 20°C (room temperature). Stirring was continued for 20 hours. The reaction

mixture was poured onto ice/water and the product was extracted with methylene chloride. The extract was washed with water, dried over sodium sulfate, and evaporated in vacuo to a volume of about 1 liter. The solution was filtered through a short column of Silica gel (1 kg). The desired product, 1,2,4,5-tetrachloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, was removed from the column with methylene chloride. Crystallization from acetone-hexane yielded 38.8 g (53%) of the title compound [mp 106-108°C; ^{1}H nmr: 1.45s (18H), 6.00s (OH), 7.75s (2H)].

12B. Formula X Where X, Y and Z are Chloro, m is 1-3 and n is 0-1

Similarly, by following the procedure of part A above and substituting for 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,

3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]pyrrole,

3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]-pyrrole, and

3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]-pyrrole,

there may be obtained the following respective compounds:

1,2,4,5-tetrachloro-3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,

1,2,4,5-tetrachloro-3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]pyrrole,

1,2,4,5-tetrachloro-3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole, and

1,2,4,5-tetrachloro-3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]pyrrole.

EXAMPLE 13
Synthesis of 2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole

13A. Formula X Where X, Y and Z are Chloro

38.8 G (0.088 mole) of 1,2,4,5-tetrachloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, as prepared in Example 12A, was suspended in 250 ml of acetone and 250 ml of acetic acid:water (4:1) and stirred. To the stirred mixture at room temperature 15.23 g (0.091 mole) of potassium iodide was added in a 10 minute period, and thereafter 11.5 g (0.091 mole) of sodium sulfite and 500 ml of water were added. Agitation was continued for 30 minutes. The precipitated solid was collected by filtration and washed with water. This solid was dissolved in ethyl acetate, dried over sodium sulfite, and evaporated *in vacuo*. The residue was recrystallized from petroleum ether to give 29.9 g (45% yield based on the starting material of Example 12A) of the title material, 2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, having physical constants identical to those obtained by the procedure of Example 10A.

13B. Formula X Where X, Y and Z are Chloro, m is 1-3 and n is 0-1

Similarly, by following the procedure of part A above and substituting for 1,2,4,5-tetrachloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

1,2,4,5-tetrachloro-3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,

1,2,4,5-tetrachloro-3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]pyrrole,

1,2,4,5-tetrachloro-3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole, and

1,2,4,5-tetrachloro-3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]pyrrole;

there may be obtained the following respective compounds:

2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzyl)-pyrrole,

2,4,5-trichloro-3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]pyrrole,

2,4,5-trichloro-3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole, and

2,4,5-trichloro-3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]pyrrole.

13C. Formula X Where X is Cl, and Y and Z are Hydrogen

A 47 g mixture containing 85 to 90% 2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, 10-12% 2,5-dichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and less than 1% of 2,3-dichloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole and 2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, prepared, for example, as described in the foregoing examples, was dissolved in 2.5 l of methylene chloride and stirred under a nitrogen atmosphere at ambient temperature (20 to 24°C), to which was added 8.0 g of solid sodium hydroxide dissolved in 800 ml of water. The stirring was continued overnight, then the aqueous and organic layers were separated. The organic layer was washed with 2.0 l of water, then washed with 1.0 l of saturated sodium chloride solution, dried over sodium sulfate, and evaporated to a residue weighing 42.3 g. HPLC analysis of the residue indicated the presence of primarily 2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, with less than 0.1% of 2,5-dichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, 2,3-dichloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole and 2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole.

The residue was recrystallized from 60 ml of acetone and 450 ml acetonitrile by refluxing and distilling off the acetone until the temperature reached 81°C. The total volume of the reaction mixture was 450 to 470 ml. The mixture was cooled with stirring overnight. The solid was filtered, washed with acetonitrile, then washed with hexane, and air dried giving 30.7 g. This was redissolved in 150 ml of acetone and filtered to remove undissolved debris, and the filter washed with 50 ml of acetone. The combined acetone was boiled at atmospheric pressure and displaced with 500 ml hexane, continuing boiling until a final volume of 350 ml was obtained, which was cooled to room temperature with stirring for 90 minutes, filtered, and the solid washed with hexane (3x50 ml), air dried, and dried in vacuo at about 40°C over night to give 28.2 g of 2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, which was determined to be 99.4% pure by HPLC analysis.

13D. Formula X Where X is Cl, and Y and Z are Hydrogen

A solution of 15 g (50 mmol) 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole and 5.5 g (27.5 mmol) Halane in 150 ml of THF was stirred under nitrogen atmosphere at room temperature for 96 hours. The bulk of the THF was evaporated in vacuo and partitioned between 1:1 ethyl acetate:hexane/10% sodium sulfite. The ethyl acetate layer was washed with water (2x200 ml), back-washed through ethyl acetate, and the combined organic layers were dried over sodium sulfate and evaporated to dryness, yielding a residue of 2-chloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole with the major impurity being 2,5-dichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, plus minor amounts of polychlorinated products.

The above obtained residue was treated with 110 ml acetic acid and 15 g Zinc dust, and vigorously stirred

under nitrogen atmosphere in a 50 to 55°C oil bath for three hours, during which period the sides of the flask were twice washed down with acetic acid. The reaction mixture was allowed to cool to room temperature, 250 ml of ethyl acetate was added, and the solid removed by filtration washing the filter cake with about 100 ml ethyl acetate. To the combined ethyl acetate was added 200 ml hexane. This was washed with water (2x200 ml), 1N HCl (1x200 ml), water (1x200 ml), saturated potassium carbonate (1x200 ml) and with water (1x200 ml), dried over sodium sulfate, and evaporated to dryness. The residue was dissolved in about 2:1 ethyl acetate:hexane with warming, and passed through a pad of 150 g silica gel (packed in 2:1 hexane: ethyl acetate) using 2:1 hexane:ethyl acetate (400 ml), followed by 1:1 hexane: ethyl acetate (400 ml) to elute the product, which was evaporated to dryness and crystallized from acetone:hexane to a boiling point of 62 to 65°C and a total volume of about 200 ml. After cooling to room temperature, the crystallized product was collected and washed with hexane and dried to afford 12.7 g of product, which was determined by HPLC to contain 97.7% 2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, 1.7% 2,3-dichloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, 0.3% 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and 0.1% 2,5-dichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole.

EXAMPLE 14
Synthesis of
2-bromo-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole

14A. Formula X Where X is Br

A cold (-70°C) solution of 2 g (6.6 mmol) of 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole in 50 ml of anhydrous methylene chloride was treated dropwise, with stirring,

with 1.067 (6.6 mmol) of bromine in 35 ml of methylene chloride. When the addition was complete, the reaction mixture was stirred for an additional hour. The solution was then poured into saturated sodium bicarbonate solution, the organic phase was separated and the aqueous phase extracted twice with methylene chloride. The combined extracts were dried and evaporated to dryness in vacuo.

Purification of the residue by tlc using hexane-ethyl acetate (80:20) as eluant, afforded 774 mg (40.5%) of the title compound, a compound according to Formula X wherein: m is 0; n is 1; R is H; X is Br; and Y and Z are both H, which was recrystallized from hexane-ethyl acetate (mp 200-201°C).

Anal. Calcd. for $C_{19}H_{24}BrNO_2$ (mw 378.296):

Theoretical:	C, 60.32; H, 6.39; N, 3.70;
Found:	C, 60.17; H, 6.37; N, 3.61.

148. Formula X Where X is Br and R is Lower Alkyl or Benzyl

Similarly, by following the procedure of part A above and substituting for 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

N-methyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-ethyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-i-propyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-butyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

and

N-benzyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

there are obtained the following respective compounds:

N-methyl-2-bromo-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole,

N-ethyl-2-bromo-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole,

N-i-propyl-2-bromo-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-butyl-2-bromo-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and

N-benzyl-2-bromo-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole.

14C. Formula X Where X is Br, m is 1-3 and n is 0-1

Similarly, by following the procedure of part A above and substituting for 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,

3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]pyrrole,

3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]-pyrrole, and

3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]-pyrrole,

there may be obtained the following respective compounds:

2-bromo-4-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,

2-bromo-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]-pyrrole,

2-bromo-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxo-ethyl]pyrrole, and

2-bromo-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxo-propyl]pyrrole.

14D. Formula X Where X is Br, R is Other Than Methyl, m is 1-3 and n is 0-1

Similarly, by following the procedure of part A above and substituting for 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

N-benzyl-3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole, and

N-ethyl-3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxo-ethyl]pyrrole;

there may be obtained the following compounds:

N-benzyl-2-bromo-4-(3,5-di-t-butyl-4-hydroxybenzyl)-pyrrole, and

N-ethyl-2-bromo-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole.

14E. Formula X Where X is I

Similarly, by following the procedure of part A above and substituting elemental iodine for elemental bromine, there is obtained 2-iodo-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, for which the variations described in parts B-D are equally applicable.

EXAMPLE 15
Synthesis of
2,3-dibromo-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole

15A. Formula X Where X and Y are Br

A solution of 2 g (6.6 mmol) of 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole in 50 ml of anhydrous methylene chloride was treated dropwise, with stirring, with a solution of 2.135 g (13.3 mmol) of bromine in 20 ml of anhydrous methylene chloride. When the addition was complete the reaction mixture was maintained at room temperature for 30 minutes further. It was then poured into saturated sodium bicarbonate solution, the organic layer was separated and the aqueous layer extracted twice with methylene chloride. The combined extracts were dried and evaporated *in vacuo*. The residue was purified by repeated tlc, using hexane:ethyl acetate (80:20) for the first development and methylene chloride for the second. There were obtained 519 mg (17%) of the title compound, a compound according to Formula X wherein: m is 0; R is H; X and Y are Br; and Z is H,, which was recrystallized from ethyl acetate-hexane (mp 231-232°C - Dec).

Anal. Calcd. for $C_{19}H_{23}Br_2NO_2$ (mw 457.197):

Theoretical:	C, 49.91; H, 5.07; N, 3.06;
Found:	C, 50.02; H, 5.00; N, 3.05.

15B. Formula X Where X and Y are Br and R is Lower Alkyl or Benzyl

Similarly, by following the procedure of part A above and substituting for 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

N-methyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-ethyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-i-propyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-butyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and
N-benzyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

there are obtained the following respective compounds:

N-methyl-2,3-dibromo-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-ethyl-2,3-dibromo-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-i-propyl-2,3-dibromo-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-butyl-2,3-dibromo-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and
N-benzyl-2,3-dibromo-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole.

15C. Formula X Where X and Y are Br, m is 1-3 and n is 0-1

Similarly, by following the procedure of part A above and substituting for 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,
3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]pyrrole,

3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]-pyrrole, and

3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]-pyrrole,

there may be obtained the following respective compounds:

2,3-dibromo-4-(3,5-di-t-butyl-4-hydroxybenzyl)-pyrrole,

2,3-dibromo-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-propyl]-pyrrole,

2,3-dibromo-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole, and

2,3-dibromo-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]pyrrole.

15D. Formula X Where X and Y are Br, R is Other Than Methyl, m is 1-3 and n is 0-1

Similarly, by following the procedure of part A above and substituting for 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

N-benzyl-3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole, and

N-ethyl-3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole;

there may be obtained the following compounds:

N-benzyl-2,3-dibromo-4-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole, and

N-ethyl-2,3-dibromo-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole.

15E. Formula X Where X and Y are I

Similarly, by following the procedure of part A above and substituting elemental iodine for elemental bromine, there is obtained 2,3-di-iodo-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, for which the variations described in parts B-D are equally applicable.

EXAMPLE 16
Synthesis of 2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole and 2,3-dithiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl) pyrrole

16A. Formula X Where Y, and/or X is SCN

A solution of thiocyanogen was prepared as follows: 3.895 g (40 mmol) of potassium thiocyanate was partially dissolved in 10 ml of anhydrous methanol, under heating. The mixture was cooled to 0°C and 3.202 g (20 mmol) of bromine in 30 ml of methylene chloride was added dropwise, stirring for 30 minutes further at room temperature.

The resultant pale yellow solution of thiocyanogen was added dropwise, at room temperature, to a solution of 3 g (10 mmol) of 3-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole in 30 ml of anhydrous dimethylformamide; the resultant pale orange solution was kept at room temperature for 1 hour, poured into water and extracted with methylene chloride. The organic extract was dried and evaporated.

Column chromatography of the residue on 150 g of silica gel, using hexane:ethyl acetate (80:20) as eluant, afforded 2.328 g (65%) of 2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, a compound according to Formula X wherein: m is 0; n is 1; R is H; X is SCN; and Y and Z are both H, (mp 230-231°C), as well as a less polar mixture.

This less polar mixture was submitted to column chromatography on 160 g of deactivated alumina (containing 3% water). The fraction eluted with hexane-ethyl acetate (80:20) afforded 300 mg (7.5%) of 2,3-dithiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

a compound according to Formula X wherein: m is 0; n is 1; R is H; X and Y are both SCN; and Z is H, (mp 143-144°C).

Both compounds were recrystallized from methylene chloride-hexane.

168. Formula X Where Y and/or X is SCN and R is Lower Alkyl or Benzyl

Similarly, by following the procedure of part A above and substituting for 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

N-methyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-ethyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-i-propyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-butyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and
N-benzyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

there are obtained the following respective compounds:

N-methyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)-4-thiocyanopyrrole,
N-methyl-2,3-dithiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-ethyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)-4-thiocyanopyrrole,
N-ethyl-2,3-dithiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-i-propyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)-4-thiocyanopyrrole,
N-i-propyl-2,3-dithiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,
N-butyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)-4-thiocyanopyrrole,
N-butyl-2,3-dithiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-benzyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)-4-thiocyanopyrrole, and

N-benzyl-2,3-dithiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole.

16C. Formula X Where Y and/or X is SCN, m is 1-3 and n is 0-1

Similarly, by following the procedure of part A above and substituting for 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,

3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]pyrrole,

3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]-pyrrole, and

3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]-pyrrole,

there are obtained the following respective compounds:

3-(3,5-di-t-butyl-4-hydroxybenzyl)-4-thiocyanopyrrole,

2,3-dithiocyano-4-(3,5-di-t-butyl-4-hydroxybenzyl)-pyrrole,

3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]-4-thiocyanopyrrole,

2,3-dithiocyano-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]pyrrole,

3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]-4-thiocyanopyrrole,

2,3-dithiocyano-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole

3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]-4-thiocyanopyrrole, and

2,3-dithiocyano-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]pyrrole.

16D. Formula X Where Y and/or X is SCN, R is Other Than Methyl, m is 1-3 and n is 0-1

Similarly, by following the procedure of part A above and substituting for 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

N-benzyl-3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole, and

N-ethyl-3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole;

there are obtained the following compounds:

N-benzyl-3-(3,5-di-t-butyl-4-hydroxybenzyl)-4-thiocyanopyrrole,

N-benzyl-2,3-dithiocyano-4-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,

N-ethyl-3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]-4-thiocyanopyrrole, and

N-ethyl-2,3-dithiocyano-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole.

EXAMPLE 17
Synthesis of N-methyl-2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole

17A. Formula X Where R is Methyl and X is Thiocyano

N-methyl-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (8 g) was dissolved in methanol (50 ml) and cooled to -70°C. A solution of thiocyanogen was prepared by the dropwise addition of a cold (-70°C) solution of bromine (6.6 g) in methanol (20 ml) to a solution of potassium thiocyanate (5.2 g) in methanol (20 ml) (also cooled to -70°C). The resulting solution of thiocyanogen was added in one portion to the cold solution of the pyrrole. The reaction mixture was allowed to warm to -40°C and was stirred for 30 minutes, keeping the temperature between

-40°C and -30°C. The solution was added to ice water and the crude product precipitated as a gum.

After decanting the water, the gum was washed well with water and then dissolved in methylene chloride, dried over sodium sulfate, and the solvent was evaporated. The residue was chromatographed on silica gel (500 g), eluting with hexane:ethyl-acetate (80:20) to yield 2.85 g of the title compound as a foam [^{1}H nmr: 1.5s (18H), 3.86s (3H), 5.68s (OH), 7.13d (1H), 7.53d (1H), 7.77s (2H); MS m/e 370 (M+)].

17B. Formula X Where X is Thiocyano and R is Benzyl or Lower Alkyl Other Than Methyl

Similarly, by following the procedure of part A above and substituting for N-methyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

N-ethyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-i-propyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-butyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and

N-benzyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

there are obtained the following respective compounds:

N-ethyl-2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-i-propyl-2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-butyl-2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and

N-benzyl-2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole.

17C. Formula X Where R is Methyl, X is SCN, m is 1-3 and n is 0-1

Similarly, by following the procedure of part A above and substituting for N-methyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

N-methyl-3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,

N-methyl-3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-propyl]pyrrole,

N-methyl-3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole, and

N-methyl-3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]pyrrole,

there are obtained the following respective compounds:

N-methyl-2-thiocyano-4-(3,5-di-t-butyl-4-hydroxy-benzyl)pyrrole,

N-methyl-2-thiocyano-4-[3-(3,5-di-t-butyl-4-hydroxy-phenyl)propyl]pyrrole,

N-methyl-2-thiocyano-4-[2-(3,5-di-t-butyl-4-hydroxy-phenyl)-1-oxoethyl]pyrrole, and

N-methyl-2-thiocyano-4-[3-(3,5-di-t-butyl-4-hydroxy-phenyl)-1-oxopropyl]pyrrole.

EXAMPLE 18
Synthesis of
2-mercapto-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole

18A. Formula X Where X is Mercapto

2-Thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole (10.0 g) was dissolved in methanol (80 ml) and cooled to -10°C. Potassium hydroxide (3.2 g) in methanol (20.0 ml) and water (20.0 ml) was added at such a rate that the temperature did not exceed 0°C. After stirring for 1 hour at the same temperature, one half of the resulting solution was converted to the title compound by acidification with 20% HCl. The product was filtered, dissolved in methylene chlorede, dried and the solvent evaporated to dryness. The residue was chromatographed on silica gel (500 g) and the product eluted with hexane: ethyl acetate (1:1) to yield 1.56 g of the purified title

compound, 2-mercapto-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole, after recrystalization from ethyl acetate-hexane [mp 213-215°C; ^{1}H nmr: 1.46s (18H), 5.46s (OH), 6.93m (1H), 7.46m (1H), 7.76s (2H), 7.91 (NH); MS m/e 331 (M+)].

Analysis calculated for $C_{19}H_{25}NO_2S$ (mw 331.45):

Theoretical:	C, 68.84; H, 7.60; N, 4.22;
Found:	C, 69.04; H, 7.38; N, 4.16.

18B. Formula X Where X, Y and/or Z is Mercapto

Similarly, by following the procedure of part A above and substituting for 2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

3-(3,5-di-t-butyl-4-hydroxybenzoyl)-4-thiocyano-pyrrole,

2,3-dithiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole, and

2,3,5-trithiocyano-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole;

there are obtained the following compounds:

3-mercapto-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole,

2,3-dimercapto-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole, and

2,3,5-trimercapto-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole.

18C. Formula X Where X is Mercapto and R is Lower Alkyl or Benzyl

Similarly, by following the procedure of part A above and substituting for 2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

N-methyl-2-thiocyano-4-(3,5-di-t-butyl-4-hydroxy benzoyl)pyrrole,

N-ethyl-2-thiocyano-4-(3,5-di-t-butyl-4-hydroxy benzoyl)pyrrole,

N-i-propyl-2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-butyl-2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and

N-benzyl-2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole;

there are obtained the following respective compounds:

N-methyl-2-mercapto-4-(3,5-di-t-butyl-4-hydroxy benzoyl)pyrrole,

N-ethyl-2-mercapto-4-(3,5-di-t-butyl-4-hydroxy benzoyl)pyrrole,

N-i-propyl-2-mercapto-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-butyl-2-mercapto-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and

N-benzyl-2-mercapto-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole.

18D. Formula X Where X, Y and/or Z is Mercapto, R is H, Lower Alkyl or Benzyl, m is 1-3 and n is 0-1

Similarly, by following the procedure of part A above and substituting for 2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzyl)-pyrrole,

N-ethyl-2,3-dithiocyano-4-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,

N-methyl-2-thiocyano-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]pyrrole,

N-benzyl-2-thiocyano-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole, and

N-methyl-2-thiocyano-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]pyrrole;

there are obtained the following respective compounds:

2-mercapto-4-(3,5-di-t-butyl-4-hydroxybenzyl)-pyrrole,

N-ethyl-2,3-dimercapto-4-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,

N-methyl-2-mercapto-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]pyrrole,

N-benzyl-2-mercapto-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole, and

N-methyl-2-mercapto-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]pyrrole.

EXAMPLE 19
Synthesis of 2-ethylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole

19A. Formula X Where X is Ethylthio

2-Thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole (2.0 g) was dissolved in ethanol (20 ml) and ethyl iodide (0.8 ml) was added with stirring. The reaction mixture was cooled to -5°C and a solution of potassium hydroxide (6.39 g) in water (5.0 ml) was added dropwise, at such a rate that the temperature did not exceed 0°C. After stirring for 1 additional hour, the reaction mixture was poured into 10% HCl (200 ml) and extracted with ethyl acetate (3x200 ml). The organic phase was washed with water (2x150 ml), dried and evaporated. The residue was purified by chromatography on alumina (3% water, 200 g) with hexane:acetone (80:20) to give 1.37 g of the pure product, which was crystallized from acetone-hexane [mp 197-199°C; ^{1}H nmr: 1.23t (3H), 1.50s (18H), 2.66c (2H), 5.63s (OH), 6.86m (1H), 7.41m (1H), 7.81s (2H), 9.36 (NH)].

Analysis calculated for $C_{21}H_{29}NO_2S$ (mw 359.50):

Theoretical:	C, 70.15;	H, 8.13; N, 3.89;
Found:	C, 70.12;	H, 8.18; N, 3.90.

19B. Formula X Where X, Y and/or Z is Ethylthio

Similarly, by following the procedure of part A above and substituting for 2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

3-(3,5-di-t-butyl-4-hydroxybenzoyl)-4-thiocyano-pyrrole,

2,5-dithiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole, and

2,3,5-trithiocyano-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole;

there are obtained the following compounds:

3-ethylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole,

2,5-diethylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole, and

2,3,5-triethylthio-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole.

19C. Formula X Where X is Ethylthio and R is Lower Alkyl or Benzyl

Similarly, by following the procedure of part A above and substituting for 2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

N-methyl-2-thiocyano-4-(3,5-di-t-butyl-4-hydroxy benzoyl)pyrrole,

N-ethyl-2-thiocyano-4-(3,5-di-t-butyl-4-hydroxy benzoyl)pyrrole,

N-i-propyl-2-thiocyano-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole,

N-butyl-2-thiocyano-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole, and

N-benzyl-2-thiocyano-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole;

there are obtained the following respective compounds:

N-methyl-2-ethylthio-4-(3,5-di-t-butyl-4-hydroxy benzoyl)pyrrole,

N-ethyl-2-ethylthio-4-(3,5-di-t-butyl-4-hydroxy benzoyl)pyrrole,

N-i-propyl-2-ethylthio-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole,

N-butyl-2-ethylthio-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole, and

N-benzyl-2-ethylthio-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole.

19D. Formula X Where X, Y and/or Z is Ethylthio, R is H, Lower Alkyl or Benzyl, m is 1-3 and n is 0-1

Similarly, by following the procedure of part A above and substituting for 2-thiocyano-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzyl)-pyrrole,

N-ethyl-2,3-dithiocyano-4-(3,5-di-t-butyl-4-hydroxy-benzyl)pyrrole,

N-methyl-2-thiocyano-4-[3-(3,5-di-t-butyl-4-hydroxy-phenyl)propyl]pyrrole,

N-benzyl-2-thiocyano-4-[2-(3,5-di-t-butyl-4-hydroxy-phenyl)-1-oxoethyl]pyrrole, and

N-methyl-2-thiocyano-4-[3-(3,5-di-t-butyl-4-hydroxy-phenyl)-1-oxopropyl]pyrrole;

there are obtained the following respective compounds:

2-ethylthio-4-(3,5-di-t-butyl-4-hydroxybenzyl)-pyrrole,

N-ethyl-2,3-diethylthio-4-(3,5-di-t-butyl-4-hydroxy-benzyl)pyrrole,

N-methyl-2-ethylthio-4-[3-(3,5-di-t-butyl-4-hydroxy-phenyl)propyl]pyrrole,

N-benzyl-2-ethylthio-4-[2-(3,5-di-t-butyl-4-hydroxy-phenyl)-1-oxoethyl]pyrrole, and

N-methyl-2-ethylthio-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]pyrrole.

19E. Formula X Where X is Methylthio and R is Lower Alkyl

Similarly, by following the procedure of part A above and substituting N-methyl-2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole for 2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and substituting methyl iodide for ethyl iodide, there is obtained N-methyl-2-methylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole [mp 173-175°C; ^{1}H nmr: 1.50s (18H), 2.3s (3H), 3.73s (3H), 5.6s (OH), 6.81m (1H), 7.38m (1H), 7.76s (2H)]. Analysis calculated for $C_{21}H_{29}NO_2S$ (mw 359.50):

Theoretical:	C, 70.15; H, 8.13; N, 3.89;
Found:	C, 69.77; H, 8.15; N, 3.75.

EXAMPLE 20

Synthesis of 3-methylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole

Formula X Where Y is Methylthio

A solution of 1.51 g (4.23 mmol) of 3-(3,5-di-t-butyl-4-hydroxybenzoyl)-4-thiocyanopyrrole in 40 ml of anhydrous methanol was treated with 0.276 ml (630 mg, 4.4 mmol) of methyl iodide. The stirred mixture was cooled to -15°C and a solution of 508 mg (12 mmol) of sodium hydroxide in 35 ml of methanol was added thereto, in a dropwise fashion. When the addition was completed the reaction mixture was kept at room temperature for 30 minutes. Dry ice was carefully added until a pH 8 was obtained. It was then poured into 200 ml of 20% sodium chloride solution, and the product extracted with methylene chloride; the extract was dried and evaporated under reduced pressure.

Purification of the residue by tlc using hexane-ethyl acetate (70:30) afforded 1.51 g (73.5%) of the title compound, a compound according to Formula X wherein: m is 0; n is 1; R is H; Y is SCH_3; and X and Z are both H, which was recrystallized from ethyl acetate-hexane (mp 175-176.5°C)

EXAMPLE 21
Synthesis of 2,3-dimethylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole

Formula X Where X and Y are Methylthio

A stirred mixture of 0.9 ml (941 mg, 9.9 mmol) of methyl disulfide and 20 ml of anhydrous methylene chloride was treated dropwise, under nitrogen atmosphere, with 0.8 ml (1.349 g, 10 mmol) of sulfuryl chloride. The resulting mixture was kept at room temperature for 1 hour and then added dropwise, under stirring, to a solution of 2 g (6.6 mmol) of 3-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole in 20 ml of anhydrous dimethylformamide. The deep brown reaction mixture was maintained for 1 additional hour at room temperature. It was then poured into water and extracted twice with methylene chloride. The combined extracts were dried and evaporated to dryness *in vacuo*.

Purificiation of the residue by tlc using hexane-ethyl acetate (80:20) gave 244 mg (9.5%) of the title compound, a compound according to Formula X wherein: m is 0; n is 1; R is H; Z is H; and X and Y are both SCH_3 (mp 222.5-223°C), which was recrystallized from methylene chloride-hexane.

EXAMPLE 22
Synthesis of 2-acetylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole

22A. Formula X Where X is Acetylthio

2-Thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole (5.0 g) and sodium acetate (40.0 g) were dissolved in acetic acid (200 ml) and acetic anhydride (200 ml). With vigorous mechanical stirring, zinc dust (21 g) was added in 3 equal portions, one every 10 minutes. During this time the temperature rose from the initial 23°C, but stayed below 30°C. Vigorous stirring was continued for 1 hour more. Then ice water (1 l) was added and the reaction mixture was stirred for another 2 hours. The precipitated product was filtered, washed well with water and then dissolved in methylene chloride, dried and the solvent evaporated to dryness. The recovered product was crystallized from methylene chloride-methanol to give 3.42 g of the purified title compound 2-acetylthio-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole (mp 223-225°C).

^{1}H nmr: 1.48s (18H), 2.35s (3H), 5.78s (OH), 6.88m (1H), 7.55m (1H), 7.78s (2H), 11.00 (NH).

Analysis calculated for $C_{21}H_{27}NO_3S$ (mw 373.49):

Theoretical:	C, 67.52; H, 7.28; N, 3.74;
Found:	C, 67.83; H, 7.46; N, 3.70.

22B. Formula X Where X, Y and/or Z is Acetylthio

Similarly, by following the procedure of part A above and substituting for 2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

3-(3,5-di-t-butyl-4-hydroxybenzoyl)-4-thiocyano-pyrrole,

2,5-dithiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole, and

2,3,5-trithiocyano-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole;

there are obtained the following compounds:

3-acetylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole,

2,5-diacetylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole, and

2,3,5-triacetylthio-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole.

22C. Formula X Where X is Acetylthio and R is Lower Alkyl or Benzyl

Similarly, by following the procedure of part A above and substituting for 2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

N-methyl-2-thiocyano-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole,

N-ethyl-2-thiocyano-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole,

N-i-propyl-2-thiocyano-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole,

N-butyl-2-thiocyano-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole, and

N-benzyl-2-thiocyano-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole;

there are obtained the following respective compounds:

N-methyl-2-acetylthio-4-(3,5-di-t-butyl-4-hydroxy benzoyl)pyrrole,

N-ethyl-2-acetylthio-4-(3,5-di-t-butyl-4-hydroxy benzoyl)pyrrole,

N-i-propyl-2-acetylthio-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole,

N-butyl-2-acetylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and

N-benzyl-2-acetylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole.

22D. Formula X Where X, Y and/or Z is Acetylthio, R is H, Lower Alkyl or Benzyl, m is 1-3 and n is 0-1

Similarly, by following the procedure of part A above and substituting for 2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzyl)-pyrrole,

N-ethyl-2,3-dithiocyano-4-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,

N-methyl-2-thiocyano-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]pyrrole,

N-benzyl-2-thiocyano-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole, and

N-methyl-2-thiocyano-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]pyrrole;

there are obtained the following respective compounds:

2-acetylthio-4-(3,5-di-t-butyl-4-hydroxybenzyl)-pyrrole,

N-ethyl-2,3-diacetylthio-4-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,

N-methyl-2-acetylthio-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]pyrrole,

N-benzyl-2-acetylthio-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole, and

N-methyl-2-acetylthio-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]pyrrole.

22E. Formula X Where X is Propionylthio

Similarly, by following the procedure of part A above and substituting propionic acid for acetic acid,

and substituting propionic anhydride for acetic anhydride, there is obtained 2-propionylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, for which the variations described in parts B-D are equally applicable.

EXAMPLE 23
Synthesis of N-methyl-2-acetylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole

Formula X Where R is Methyl and X is Acetylthio

N-Methyl-2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (2.69 g) and sodium acetate (21.0 g) were dissolved in acetic acid (100 ml) and acetic anhydride (100 ml). With vigorous mechanical stirring, zinc dust (11 g) was added in portions. After stirring for 90 minutes, the reaction mixture was poured into ice water (1 l). The solution was extracted with methylene chloride (4x300ml). The combined organic layers were washed with water (3x500 ml), dried and evaporated to give 2.8 g of the crude product.

The crude product was purified by preparative tlc on silica gel plates, eluting with hexane:ethyl acetate (75:25), and repurified in the same manner with 80:20 hexane:ethyl acetate. The recovered product (1.4 g) was crystallized from acetone-hexane to afford 0.77 g of the purified title compound, N-methyl-2-acetylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole [mp 120-123°C; ^{1}H nmr: 1.5s (18H), 2.41s (3H), 3.63s (3H), 5.63s (OH), 6.91m (1H), 7.51m (1H), 7.8s (2H); MS m/e 387 (M+)].

EXAMPLE 24
Synthesis of 2-methylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole

24A. Formula X Where X is Methylsulfinyl

2-Methylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole (4.0 g) was dissolved in methylene chloride (100 ml) and cooled in ice. A solution of m-chloroperbenzoic acid (2.48 g) in methylene chloride (100 ml) was added dropwise with stirring. After stirring for an additional 30 minutes, the mixture was poured into a saturated sodium bicarbonate solution (200 ml). After separation of the organic layer, the aqueous phase was extracted with methylene chloride (300 ml) and then with ethyl acetate (300 ml). The combined organic extracts were dried and evaporated to dryness and the residue was recrystallized from methanol-methylene chloride to afford 4.10 g of the purified title product, 2-methylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (a compound according to Formula X wherein: m is 0; n is 1; R is H; X is $SOCH_3$; and Y and Z are both H) (mp 201-202.5°C).

24B. Formula X Where X, Y and/or Z is Methylsulfinyl

Similarly, by following the procedure of part A above and substituting for 2-methylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

3-methylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole,

2,5-dimethylthio-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole, and

2,3,5-trimethylthio-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole;

there are obtained the following compounds:

3-methylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole,

2,5-dimethylsulfinyl-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole, and

2,3,5-trimethylsulfinyl-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole.

24C. Formula X Where X is Methylsulfinyl and R is Lower Alkyl or Benzyl

Similarly, by following the procedure of part A above and substituting for 2-methylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

N-methyl-2-methylthio-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole,

N-ethyl-2-methylthio-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole,

N-i-propyl-2-methylthio-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole,

N-butyl-2-methylthio-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole, and

N-benzyl-2-methylthio-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole;

there are obtained the following respective compounds:

N-methyl-2-methylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-ethyl-2-methylsulfinyl-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole,

N-i-propyl-2-methylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-butyl-2-methylsulfinyl-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole, and

N-benzyl-2-methylsulfinyl-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole.

24D. Formula X Where X, Y and/or Z is Methylsulfinyl, R is H, Lower Alkyl or Benzyl, m is 1-3 and n is 0-1

Similarly, by following the procedure of part A above and substituting for 2-methylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

2-methylthio-4-(3,5-di-t-butyl-4-hydroxybenzyl)-pyrrole,

N-ethyl-2,3-dimethylthio-4-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,

N-methyl-2-methylthio-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]pyrrole,

N-benzyl-2-methylthio-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole, and

N-methyl-2-methylthio-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]pyrrole;

there are obtained the following respective compounds:

2-methylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzyl)-pyrrole,

N-ethyl-2,3-dimethylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,

N-methyl-2-methylsulfinyl-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]pyrrole,

N-benzyl-2-methylsulfinyl-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole, and

N-methyl-2-methylsulfinyl-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]pyrrole.

24E. Formula X Where X is Ethylsulfinyl

Similarly, by following the procedure of part A above and substituting 2-ethylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole for 2-methylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, there is obtained 2-ethylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, for which the variations described in parts 22B-D are equally applicable.

EXAMPLE 25
Synthesis of 2-methylsulfonyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole

25A. Formula X Where X is Methylsulfonyl

2-Methylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole (2.0 g) was dissolved in methylene chloride (40 ml) and a solution of m-chloroperbenzoic acid (1.2 g) was added. After stirring at room temperature for 30 minutes, the mixture was poured into a saturated sodium bicarbonate solution (100 ml). After separation of the organic layer, the aqueous phase was extracted with methylene chloride (300 ml). The combined organic extracts were dried and evaporated to dryness and the residue was recrystallized from ethyl acetate-hexane to afford 2.05 g of the purified title product, 2-methylsulfonyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (a compound according to Formula X wherein: m is 0; n is 1; R is H; X is SO_2CH_3; and Y and Z are both H) (mp 237-238°C).

25B. Formula X Where X, Y and/or Z is Methylsulfonyl

Similarly, by following the procedure of part A above and substituting for 2-methylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

3-methylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole,

2,5-dimethylsulfinyl-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole, and

2,3,5-trimethylsulfinyl-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole;

there are obtained the following compounds:

3-methylsulfonyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole,

2,5-dimethylsulfonyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and

2,3,5-trimethylsulfonyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole.

25C. Formula X Where X is Methylsulfonyl and R is Lower Alkyl or Benzyl

Similarly, by following the procedure of part A above and substituting for 2-methylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

N-methyl-2-methylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-ethyl-2-methylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-i-propyl-2-methylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-butyl-2-methylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and

N-benzyl-2-methylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole;

there are obtained the following respective compounds:

N-methyl-2-methylsulfonyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-ethyl-2-methylsulfonyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-i-propyl-2-methylsulfonyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-butyl-2-methylsulfonyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, and

N-benzyl-2-methylsulfonyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole.

25D. Formula X Where X, Y and/or Z is Methylsulfonyl, R is H, Lower Alkyl or Benzyl, m is 1-3 and n is 0-1

Similarly, by following the procedure of part A above and substituting for 2-methylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

2-methylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzyl)-pyrrole,

N-ethyl-2,3-dimethylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,

N-methyl-2-methylsulfinyl-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]pyrrole,

N-benzyl-2-methylsulfinyl-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole, and

N-methyl-2-methylsulfinyl-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]pyrrole.

there are obtained the following respective compounds:

2-methylsulfonyl-4-(3,5-di-t-butyl-4-hydroxybenzyl)-pyrrole,

N-ethyl-2,3-dimethylsulfonyl-4-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,

N-methyl-2-methylsulfonyl-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]pyrrole,

N-benzyl-2-methylsulfonyl-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole, and

N-methyl-2-methylsulfonyl-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]pyrrole.

25E. Formula X Where X is Ethylsulfonyl

Similarly, by following the procedure of part A above and substituting 2-ethylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole for 2-methylsulfinyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, there is obtained 2-ethylsulfonyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, for which the variations described in parts 23B-D are equally applicable.

EXAMPLE 26
Synthesis of 2-methylsulfonyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole

26A. Formula X Where X is Methylsulfonyl

2-Methylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole (4.0 g) is dissolved in methylene chloride (100 ml) and cooled in ice. A solution of m-chloroperbenzoic acid (5.0 g) in methylene chloride (100 ml) is added dropwise with stirring. After stirring for an additional 2 hours, the mixture is poured into a saturated sodium bicarbonate solution (200 ml). After separation of the organic layer, the aqueous phase is extracted with methylene chloride (300 ml) and then with ethyl acetate (300 ml). The combined organic extracts are dried and evaporated to dryness and the residue is recrystallized from methanol-methylene chloride to afford the purified title product, 2-methylsulfonyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, m.p. 237-238°C, (a compound according to Formula X wherein: m is 0; n is 1; R is H; X is SO_2CH_3; and Y and Z are both H).

26B. Formula X Where X, Y and/or Z is Methylsulfonyl

Similarly, by following the procedure of part A above and substituting for 2-methylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

3-methylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole,

2,5-dimethylthio-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole, and

2,3,5-trimethylthio-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole;

there are obtained the following compounds:

3-methylsulfonyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole,

2,5-dimethylsulfonyl-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole, and

2,3,5-trimethylsulfonyl-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole.

26C. Formula X Where X is Methylsulfonyl and R is Lower Alkyl or Benzyl

Similarly, by following the procedure of part A above and substituting for 2-methylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

N-methyl-2-methylthio-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole,

N-ethyl-2-methylthio-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole,

N-i-propyl-2-methylthio-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole,

N-butyl-2-methylthio-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole, and

N-benzyl-2-methylthio-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole;

there are obtained the following respective compounds:

N-methyl-2-methylsulfonyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-ethyl-2-methylsulfonyl-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole,

N-i-propyl-2-methylsulfonyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-butyl-2-methylsulfonyl-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole, and

N-benzyl-2-methylsulfonyl-4-(3,5-di-t-butyl-4-hydroxy-benzoyl)pyrrole.

26D. Formula X Where X, Y and/or Z is Methylsulfonyl, R is H, Lower Alkyl or Benzyl, m is 1-3 and n is 0-1

Similarly, by following the procedure of part A above and substituting for 2-methylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

2-methylthio-4-(3,5-di-t-butyl-4-hydroxybenzyl)-pyrrole,

N-ethyl-2,3-dimethylthio-4-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,

N-methyl-2-methylthio-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]pyrrole,

N-benzyl-2-methylthio-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole, and

N-methyl-2-methylthio-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]pyrrole;

there are obtained the following respective compounds:

2-methylsulfonyl-4-(3,5-di-t-butyl-4-hydroxybenzyl)-pyrrole,

N-ethyl-2,3-dimethylsulfonyl-4-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,

N-methyl-2-methylsulfonyl-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]pyrrole,

N-benzyl-2-methylsulfonyl-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole, and

N-methyl-2-methylsulfonyl-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]pyrrole.

26E. Formula X Where X is Ethylsulfonyl

Similarly, by following the procedure of part A above and substituting 2-ethylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole for 2-methylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, there is obtained 2-ethylsulfonyl-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, for which the variations described in parts 24B-D are equally applicable.

EXAMPLE 27
Synthesis of
3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole

27A. Formula X Where m is 1 and n is 0

A solution of 1 g (3 mmol) of 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole in 100 ml of anhydrous tetrahydrofuran (THF) was treated portionwise with 1 g (26 mmol) of lithium aluminum hydride (LAH). The reaction mixture was refluxed for 4 hours, cooled and poured into saturated sodium chloride solution. It was then extracted twice with methylene chloride. The combined extracts were dried and evaporated under reduced pressure.

The solid residue was purified on a chromatograph using hexane-ethyl acetate (80:20), to afford 935 mg (98%) of the title compound, a compound according to Formula X wherein: m is 1; n is 0; R is H; X, Y and Z are each H, which was recrystallized from hexane-pentane (mp 77.5-78°C).

Analysis Calculated for $C_{19}H_{27}NO$ (mw 285.417):

Theoretical:	C, 79.94; H, 9.53; N, 4.90;
Found:	C, 79.86; H, 9.51; N, 4.85.

27B. Formula X Where m is 2-3 and n is 0

Similarly, by following the procedure of part A above and substituting for 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]-pyrrole, and

3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]-pyrrole;

there are obtained the following respective compounds:

3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)ethyl]pyrrole, and

3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]pyrrole.

27C. Formula X Where m is 1-3, n is 0, and R is Lower Alkyl or Benzyl

Similarly, by following the procedure of part A above and substituting for 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

N-methyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

N-ethyl-3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole,

N-i-propyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole,

N-s-butyl-3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]pyrrole; and

N-benzyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole,

there are obtained the following respective compounds:

N-methyl-3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,

N-ethyl-3-[2-(3,5-di-t-butyl-4-hydroxyphenyl)ethyl]-pyrrole,

N-i-propyl-3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole,

N-s-butyl-3-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-propyl]pyrrole; and

N-benzyl-3-(3,5-di-t-butyl-4-hydroxybenzyl)pyrrole.

27D. Formula X Where m is 1-3, n is 0, R is Hydrogen, Lower Alkyl or Benzyl, and X, Y and/or Z is Lower Alkyl

Similarly, by following the procedure of part A above and substituting for 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

2,5-dimethyl-3-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole,

N-ethyl-2-ethyl-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole, and

N-benzyl-3-methyl-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]pyrrole;

there are obtained the following respective compounds:

2,5-dimethyl-3-(3,5-di-t-butyl-4-hydroxybenzyl)-pyrrole,

N-ethyl-2-ethyl-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-ethyl]pyrrole, and

N-benzyl-3-methyl-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]pyrrole.

27E. Formula X Where m is 1-3, n is 0, R is Hydrogen, Lower Alkyl or Benzyl, and X, Y and/or Z is Halo

Similarly, by following the procedure of part A above and substituting for 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

2,3-dibromo-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole,

N-methyl-2-chloro-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxoethyl]pyrrole, and

N-benzyl-2,5-dichloro-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)-1-oxopropyl]pyrrole;

there are obtained the following respective compounds:

2,3-dibromo-4-(3,5-di-t-butyl-4-hydroxybenzyl)-pyrrole,

N-methyl-2-chloro-4-[2-(3,5-di-t-butyl-4-hydroxyphenyl)ethyl]pyrrole, and

N-benzyl-2,5-dichloro-4-[3-(3,5-di-t-butyl-4-hydroxyphenyl)propyl]pyrrole.

27F. Formula X Where m is 1-3, n is 0, R is Hydrogen, Lower Alkyl, or Benzyl, and X, Y and/or Z is Mercapto or Lower Alkylthio

Similarly, by following the procedure of part A above and substituting for 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole the following starting materials:

2-mercapto-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole, and

3-methylthio-4-(3,5-di-t-butyl-4-hydroxybenzoyl)-pyrrole;

there are obtained the following respective compounds:

2-mercapto-4-(3,5-di-t-butyl-4-hydroxybenzyl)-pyrrole, and

3-methylthio-4-(3,5-di-t-butyl-4-hydroxybenzyl)-pyrrole.

EXAMPLE 28
Synthesis of 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole-N-acetic acid

28A. Formula X Where R is CH_2COOH

3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (2.0 g) was added to a cooled, stirred suspension of sodium hydride (50%, 1.02 g) in DMF (90.0 ml) under nitrogen. After stirring for 1 hour at 20-23°C, bromoacetic acid (1.12 g) was added and the mixture was stirred at room temperature for 20 hours. The mixture was poured into ice water (300 ml) and concentrated HCl (4.0 ml) was added. Then, the reaction mixture was extracted with ethyl acetate (3x250 ml). The organic layer was washed with water (5x200 ml), dried and evaporated to dryness. The product was isolated by conventional means, and obtained as an oil [U.V. (ETOH) 293 nm (ε 12,900); IR ($CHCL_3$ 3623, 1739, 1621 cm^{-1}; NMR ($CDCL_3$) 1.43(s, 18H), 4.66 (s, 2H), 5.65 (broad singlet, COOH), 7.40 (m, 1H), 7.81 (s, 2H)].

28B. Formula X Where R is $(CH_2)_2COOH$

Similarly, by following the procedure of part A above and substituting chloropropionic acid for bromoacetic acid, there is obtained 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole-N-propionic acid.

EXAMPLE 29
Synthesis of 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole-N-acetic acid dicyclohexylamine salt

29A. The Dicyclohexylamine Salt of Formula X Where R is CH_2COOH

The product obtained as an oil in Example 28A was converted to its dicyclohexylamine salt directly by dissolving the acid in methylene chloride (50.0 ml) and adding dicyclohexylamine (1.4 ml). Upon evaporation to dryness, the residue was recrystallized from ethyl acetate-hexane to give 2.1 g of the purified desired product. An analytical sample was prepared by recrystallization from methanol-ethyl acetate (mp 178-179°C).

^1H nmr: 1.48m (18H), 4.46s (2H), 5.6s (OH), 6.65m (2H), 7.26m (1H), 7.80s (2H).

Anal. Calcd. for $C_{33}H_{50}N_2O_4$ (mw 547.76):

Theoretical:	C, 72.35; H, 8.90;
Found:	C, 72.27; H, 8.59.

EXAMPLE 30
Adjuvant-Induced Arthritis Assay "AI"

Anti-inflammatory activity is determined by the Adjuvant-Induced Arthritis ("AI") Assay, as is well accepted in the art. A modification of the assay

described by Pearson, et al., supra., is performed as follows:

Female Hla:(SD) BR rats weighing 160-180 g are randomly distributed to treatment groups of 12 animals, and given food and water ad libitum. Test materials are prepared fresh weekly as suspensions in carboxymethyl cellulose. The test animals are orally dosed with the suspensions in volumes of 1 ml twice per day Monday through Friday, and with 2 ml once per day on Saturdays and Sundays. A control group does not receive the test materials. At time 0, rats are injected intradermally in the proximal quarter of the tail with 0.1 ml of a mineral oil suspension of heat-killed Mycobacterium butyricum (Difco) at a concentration of 10 mg/ml. On day 18 the intensity of swelling in the four paws and tail is estimated visually and scored (0-4 for paws, 0-3 for tail) such that the total maximum score, indicating intense swelling of all four paws and tail, is 19. The animals are then sacrificed; the hind paws of each animal are removed and weighed. The percent inhibition is calculated by comparing the weight increase of the hind paws of the test animals versus the control animals.

EXAMPLE 31

Adjuvant-Induced Arthritis Assay Using 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole

The "AI" assay, as described in Example 30, was performed using 3-(3,5-di-t-butyl-4-hydroxybenzoyl) pyrrole (prepared according to Example 2) as the test material.

A daily dose of 0.4 mg/kg of body weight resulted in a 54% inhibition of hind paw weight increase, and a daily dose of 2.0 mg/kg of body weight resulted in a 70% inhibition of hind paw weight increased, as compared to

control animals that did not receive the 3-(3,5-di-t-butyl-4-hydroxybenzoyl) pyrrole.

The following compounds are compounds of formula X' wherein R is hydrogen, m is 0, n is 1 and the following are substituents for X, Y, and Z

X	Y	Z	Dosage(mg/kg)	% Inhibition
H	H	H	0.4	54
			2.0	70
Cl	H	H	2.0	16
Cl	Cl	Cl	2.0	34
SCN	H	H	0.4	41
			2.0	47

EXAMPLE 32
Carrageenan-Induced Rat Paw Inflammation Assay "CI"

Anti-inflammatory activity is determined by the Carrageenan-Induced Rat Paw Inflammation "CI" Assay, as is well accepted in the art. A modification of the assay described by Winter, et al., supra., is performed as follows:

Female albino rats (Sim: (SD)fbr) weighing 80-90 g receive the test materials orally in 1 ml aqueous solution at hour 0. One hour later (hr 1) 0.05 ml of a 1% solution (in aqueous 0.9% NaCl) of carrageenan is injected into the right hind paw to inflame the paw. The rats are sacrificed at hour 4, at which time both hind paws are removed and individually weighed. The percent increase in the weight of the inflamed paw over that of the opposite non-inflamed paw is calculated, and the results are reported according to the formula:

$$\frac{\text{wt right paw - wt left paw}}{\text{wt left paw}} \times 100 = \% \text{ increase.}$$

% Inhibition is determined by comparing the % increase in test animals vs. control animals, for example, for the following compounds of formula X' wherein R is hydrogen, m is 0, n is 1 and the following are substituents for X, Y, and Z:

X	Y	Z	Dosage(mg/kg)	% Inhibition
H	H	H	1.0	24
			10.0	44
Cl	H	H	3.0	33
			15.0	36
Cl	Cl	Cl	3.0	26
			15.0	59
SCN	H	H	3.0	43
			15.0	53

EXAMPLE 33

Arachidonic Acid-Induced Mouse Ear Edema Assay "AAI"

Topical anti-inflammatory activity is determined by the Arachidonic Acid-Induced Mouse Ear Edema "AAI" Assay, as is well accepted in the art. A modification of the assay described by Young, et al., supra., is performed as follows:

The test materials are prepared as solutions in acetone and applied to the right ears of mice, in groups of eight (8), at hour 0. At hour 1, 2 mg of arachidonic acid in acetone solution is applied to the right ears of the mice to induce an inflammatory response. The left ears of these animals serve as negative controls. At hour 2 the mice are sacrificed; their ears are removed and 8 mm diameter full thickness plugs are cut from the tip of each ear. The plugs are weighed and the mean right and left plug weights are calculated for each

group. The results are expressed as percent inhibition of ear plug weight increase relative to a positive control group receiving only acetone at hour 0.

The following data was obtained using compounds of formula X' wherein R is hydrogen, m is 0, n is 1 and the following are substituents for X, Y, and Z:

X	Y	Z	Dosage(mg/ear)	% Inhibition
H	H	H	0.5	49
			1.0	62
			2.0	67
Cl	H	H	2.0	26
Cl	Cl	Cl	2.0	18

EXAMPLE 34
Phenylquinone-Induced Mouse Writhing Assay "PI"

Analgetic activity is determined by the Phenylquinone-Induced Mouse Writhing "PI" Assay, as is well accepted in the art. Cyclooxygenase inhibitors are known to be active in this assay. A modification of the assay described by Hendershot, et al., supra., is performed as follows:

Phenylquinone solution is prepared as follows: 4 mg of phenylquinone is dissolved in 0.5 ml of absolute ethanol, after which 19.5 ml of warmed distilled water is added. When properly prepared, all of the phenylquinone solution remains in solution. The solution is used soon after preparation

The test materials are administered orally in 0.2 ml of an aqueous vehicle at hour 0 to groups of eight male Swiss-Webster (Simonsen) mice weighing about 18-20 g. At either twenty (20) minutes or one hundred twenty (120)

minutes later, 0.25 ml of a 0.02% solution of phenylquinone is injected into each animal, to induce writhing. The animals are then observed for the next ten (10) minutes for writhing responses, and the number of writhes per animal is recorded. The mean number of writhes is calculated for each treatment group and the results are expressed as percent inhibition of writhing responses relative to a control group receiving vehicle alone.

The following data was obtained using compounds of formula X' wherein R is hydrogen, m is 0, n is 1 and the following are substituents for X, Y, and Z:

X	Y	Z	Time (min)	Dosage(mg/kg)	% Inhibition
H	H	H	20	0.1	15
				1.0	61
				1.5	100
				5.0	99
				15.0	97
			120	15.0	100
Cl	H	H	20	3.0	5
				15.0	58
				50.0	63
			120	15.0	99
Cl	Cl	Cl	20	3.0	13
				15.0	24
				50.0	36
SCN	H	H	20	3.0	57
				15.0	78
				50.0	93
			120	15.0	97

EXAMPLE 35
Human Polymorphonuclear Leukocyte Assay "HPMN"

Lipoxygenase inhibition activity is determined in vitro by the Human Polymorphonuclear Leukocyte ("HPMN") Assay, as is well accepted in the art. A modification of the assay described by Radmark, et al., supra., is performed as follows:

1. Preparation of the cells: The HPMNs are prepared from 200-300 ml of heparinized blood of healthy donors not receiving any medication for at least 7 days, using Ficol-Hypaque gradients. In general, HPMNs are greater than 90% pure and their viability is assessed by dye-exclusion to be better than 95%. The cells are suspended in phosphate buffered saline containing 1.0 mM $CaCl_2$ (PH 7.4) and 0.1% ovalbumin, and used within 30 minutes.

2. Lipoxygenase Assay: Incubations are carried out at 37°C for 5 minutes in a total volume of 0.2 ml arachidonic acid 1-C^{14} ($1x10^{-4}$M unless otherwise indicated, and approximately 300,000 cpm) is added to a suspension of cells (ca $5x10^6$) to initiate the reaction. Prior to the addition of above substrate, the test substances are added to the cells at appropriate concentrations and pre-incubated at 37°C for 5 minutes. In general, stock solutions of test substances are prepared in ethanol (or other appropriate solvents) and diluted with either incubation-buffer or water. The final concentration of ethanol in the incubation does not exceed 1%. Boiled enzyme blanks and controls containing no test compound are always included. The incubations are terminated by the addition of 0.6 ml of methanol, vortexed and kept on ice for 30 minutes.

1.6 Ml of deionized water is added, vortexed, and centrifuged. The supernatants are decanted and kept in the freezer overnight. Separation of arachidonic acid and lipoxygenase products are carried out using "Baker" disposable C^{-18} extraction columns (1 ml capacity). The columns are prewashed with MeOH (2.0 ml) followed by deionized water (2 ml). After most of the solvent is removed, 2.0 ml of the supernatant is applied to the extraction columns and the solvent is allowed to flow through. The columns are then washed with 5 ml of deionized water and the eluate is discarded. The columns are then eluted with 6.0 ml of a solvent mixture (acetonitrite:H_2O:acetic acid in the proportion 50:50:0.1) which recovers all the arachidonic acid metabolites including 5-HETE and LTB_4 with very little of arachidonic acid (AA) being eluted (less than 2-3% of incubated counts). The columns are then eluted with 2.0 ml of methanol (forced through by N_2) which elutes all of the unreacted substrate AA. The eluates are collected in scintillation vials and 1.0 ml aliquots from each of the two fractions are counted for radioactivity in a Packard liquid scintillation counter. From the radioactivity data thus obtained percent yields of total lipoxygenase products in blanks, controls and drug-containing tubes are calculated as well as percent inhibition by the test compounds.

The following data was obtained using compounds of formula X' wherein R is hydrogen, m is 0, n is 1 and the following are substituents for X, Y, and Z.

X	Y	Z	Amt for 50% Inhibition
Cl	H	H	5.9μM
Cl	Cl	Cl	5.4μM
SCN	H	H	27 μM

EXAMPLE 36
Synthesis of
2-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole

3,5-Di-t-butyl-4-hydroxybenzoic acid (0.5 g) was suspended in 20 ml of dry methylene chloride and 300 mg of thionyl chloride was added, followed by 7 drops of dry dimethylformamide. All dissolved rapidly at room temperature. After 20 minutes, a sample treated with methanol showed no acid left. The solution was evaporated to dryness, then azeotropically distilled twice with benzene to remove excess thionyl chloride. The residue was dissolved in benzene, 2 ml pyrrole was added and the mixture was refluxed for 30 minutes. 2 Ml more of pyrrole was added and the mixture was refluxed for 1 hour more. After cooling, the mixture was added to a short SiO_2 column and eluted with benzene. Elution with CH_2Cl_2 gave the product, 0.325 g (54%), homogeneous on tlc.

A repetition of the reaction using the acid chloride derived from 3.0 g of acid, and a total of 24 ml pyrrole in 125 ml benzene for a total reflux time of 2.5 hours gave 1.61 g homogeneous product (mp 145.5-146.5°C). Analysis calculated for $C_{19}H_{25}NO_2$ (m.w. 299.398):

Theoretical:	C, 76.22; H, 8.42; N, 4.68;
Found:	C, 76.02; H, 8.16; N, 4.72.

EXAMPLE 37
Comparison of
3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole
with
2-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole

Side by side studies were undertaken to compare the anti-inflammatory activity of 3-(3,5-di-t-butyl-4-

hydroxybenzoyl)pyrrole (material "A", a compound of this invention prepared according to Example 2A) with that of 2-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole (material "B", a known compound prepared according to Example 36). The assays described in Examples 32-35 were performed using materials "A" and "B", and the results are reported below in Table I.

Table I

	"A"		"B"	
Assay	Dose	Inhibition	Dose	Inhibition
CI	1.0 mg/kg	24%	100.0 mg/kg	30%
	10.0 mg/kg	44%		
AAI	0.5 mg/ear	49%	2.0 mg/ear	22%
	1.0 mg/ear	62%		
	2.0 mg/ear	67%		
	2.0 mg/ear	69%		
PI				
(20 min)	0.1 mg/kg	15%	5.0 mg/kg	26%
	1.0 mg/kg	61%	15.0 mg/kg	40%
	1.5 mg/kg	100%	15.0 mg/kg	52%
	5.0 mg/kg	99%	15.0 mg/kg	65%
	15.0 mg/kg	97%	50.0 mg/kg	56%
	15.0 mg/kg	96%	50.0 mg/kg	38%
(120 min)	15.0 mg/kg	100%	15.0 mg/kg	49%
HPMN	28.0 µM	50%	36.0 µM	50%

The results shown in Table 1 demonstrate that the anti-inflammatory activity of the present invention (exemplified by material "A") is greatly enhanced over the closest known anti-inflammatory agents (exemplified by material "B").

EXAMPLE 38

Formulations

The following example illustrates the preparation of representative pharmaceutical formulations containing an

active compound of Formula X', e.g., 3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole.

38A. I.V. Formulation

Active compound		0.1 g
Propylene glycol		20.0 g
Polyethylene glycol 400		20.0 g
Tween 80		1.0 g
0.9% Saline solution	qs	100.0 mL

The active compound is dissolved in propylene glycol, polyethylene glycol 400 and Tween 80. A sufficient quantity of 0.9% saline solution is then added with stirring to provide 100 mL of the I.V. solution which is filtered through a 0.2 micron membrane filter and packaged under sterile conditions.

38B. Tablet Formulation

	parts by weight
Active compound	5.0
Magnesium stearate	0.75
Starch	0.75
Lactose	29.0
PVP (polyvinylpyrrolidone)	0.75

The above ingredients are combined and granulated using methanol as the solvent. The formulation is then dried and formed into tablets (containing 2 mg of active compound) with an appropriate tabletting machine.

38C. Formulations With Other Active Ingredients

Other compounds of Formula X', such as those prepared in accordance with Examples 2-29, can be used as the active compound in the preparation of the formulations of this example.

EXAMPLE 39

IL-1β Induced Bone Resorption Inhibition Assay

IL-1β induced bone resorption inhibition is determined in vitro according to the assay described by Chin et al., supra., as is well accepted in the art. A modification of that assay is performed as follows:

^{45}Ca prelabelled rat fetal long bones are dissected and cultured in Linbro dishes (one radius and one ulna per well) at 37°C overnight in BGJ_b medium, supplemented with 1 mg/ml of bovine serum albumin ("BSA"). All assays are performed using five pairs of bones per dosage and control group, as follows:

A. Test - ^{45}Ca bones, medium, test compound dissolved in the same culture medium (to a desired concentration, e.g., $1.0x10^{-9}$ M to $4.0x10^{-8}$ M), and IL-1β (at a concentration within the range of 50 to 500 pg/ml);

B. Background Control - ^{45}Ca bones and medium only - to measure spontaneous release of ^{45}Ca from the bones into the medium;

C. Basal Control - ^{45}Ca bones, medium, and test compound (one group per each concentration tested) - to measure compound inhibition of spontaneous release of ^{45}Ca from the bones; and

D. Untreated Control - ^{45}Ca bones, medium, and IL-1β (at the concentration used for the Test groups) - to measure IL-1β induced release of ^{45}Ca from the bones.

On day 1, the above groups are prepared in the Linbro dishes and incubated at 37°C. Incubation is continued until day 6, with one medium change and data collection at the end of day 3.

^{45}Ca in the culture medium is counted from the culture medium in each well using a scintillation counter at the end of day 3 and similarly counted at the end of

day 6, after which the remaining bones are digested with 0.1 N HCl and the ^{45}Ca present in the bone digest is also counted. Total ^{45}Ca is computed by adding the ^{45}Ca in the bone digest plus the ^{45}Ca detected in the culture medium. The results are expressed as a percentage of ^{45}Ca released from each pair of bones relative to total ^{45}Ca.

The Background Controls (B) are measured to determine the level of spontaneous ^{45}Ca release not attributable to the IL-1β (usually about 10 to 15%). The background release value obtained is subtracted from the values obtained for the Test (A) and Untreated Control (D) groups, to give the net % of ^{45}Ca released due to IL-1β treatment (the "Net % Untreated" for group D).

The Basal Controls (C) are measured to determine the level of spontaneous ^{45}Ca release inhibition attributable to the test compound at each concentration tested. The basal inhibition values obtained are used as negative controls for the corresponding Test group, subtracting the basal inhibition from the values for each corresponding test group to give a net % of ^{45}Ca IL-1β-induced inhibition for each test compound (the "Net % Test").

The results for the overall assay are expressed as mean % inhibition ± sem. of ^{45}Ca released due to test compound treatment (the "% Inhibition"), which is calculated according to the following formula:

$$\frac{\text{Net \% Untreated - Net \% Test}}{\text{Net \% Untreated}} \times 100 = \text{\% Inhibition}$$

The concentration for 50% inhibition (IC_{50}) is also determined.

Compounds of the present invention were tested according to the above-described method and the results

are reported below in Table II, demonstrating the ability to inhibit IL-1β induced bone resorption. The compounds tested were:

A. 2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, prepared, for example, as described in Example 16;

B. 2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, prepared, for example, as described in Example 10 or 13; and

C. 2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, prepared, for example, as described in Example 9 or 11.

Also tested were known anti-bone resorptive agents naproxen and thionaphthene-2-carboxylic acid ("TNCA").

Table II

Compound	Dose	% Inhibition	IC_{50}
Naproxen	$1x10^{-6}$	101.98 ± 5.88	$3.0x10^{-7}$
	$5x10^{-7}$	63.77 ± 13.11	
	$1x10^{-7}$	11.65 ± 19.49	
TNCA	$1x10^{-4}$	78.76 ± 2.46	$3.0x10^{-5}$
	$5x10^{-5}$	67.99 ± 5.08	
	$1x10^{-5}$	13.84 ± 11.67	
A	$1x10^{-5}$	95.27 ± 4.50	$3.0x10^{-8}$
	$5x10^{-6}$	87.85 ± 4.85	
	$1x10^{-6}$	92.82 ± 4.83	
	$5x10^{-7}$	90.82 ± 5.96	
	$1x10^{-7}$	88.91 ± 7.49	
	$3x10^{-8}$	49.82 ± 9.40	
B	$1x10^{-5}$	100.42 ± 5.37	$3.3x10^{-8}$
	$1x10^{-6}$	101.17 ± 6.51	
	$1x10^{-7}$	76.09 ± 10.14	
	$1x10^{-8}$	9.75 ± 9.13	
C	$1x10^{-7}$	91.26 ± 6.87	$1.7x10^{-9}$
	$1x10^{-8}$	90.67 ± 5.54	
	$1x10^{-9}$	34.76 ± 11.51	
	$1x10^{-10}$	0.27 ± 13.63	

EXAMPLE 40

PTH Induced Bone Resorption Inhibition Assay

PTH induced bone resorption inhibition is determined in vitro according to the assays described by Raisz et al., supra., as is well accepted in the art. A modification of that assay is performed as follows: ^{45}Ca prelabelled rat fetal long bones are dissected and cultured (one radius and one ulna per well) in Linbro dishes at 37°C overnight in BGJ_b medium, supplemented with 1 mg/ml of BSA. All assays are performed using five pairs of bones per dosage and control group, as follows:

A. Test - ^{45}Ca bones, medium, test compound dissolved in the same culture medium (to a desired concentration, e.g., $1.0x10^{-9}$ M to $4.0x10^{-8}$ M), and bPTH(1-34) ($2.4x10^{-6}$ M);

B. Background Control - ^{45}Ca bones and medium only - to measure spontaneous release of ^{45}Ca from the bones into the medium;

C. Basal Control - ^{45}Ca bones, medium, and test compound (one group per each concentration tested) - to measure compound inhibition of spontaneous release of ^{45}Ca from the bones; and

D. Untreated Control - ^{45}Ca bones, medium, and bPTH (at the concentration used for the Test groups) - to measure bPTH induced release of ^{45}Ca from the bones.

On day 1, the above groups are prepared in the Linbro dishes and incubated at 37°C. Incubation is continued until day 6, with one medium change and data collection at the end of day 3.

^{45}Ca in the culture medium is counted from the culture medium in each well using a scintillation counter at the end of day 3 and similarly counted at the end of day 6, after which the remaining bones are digested with

0.1 N HCl and the ^{45}Ca present in the bone digest is also counted. Total ^{45}Ca is computed by adding the ^{45}Ca in the bone digest plus the ^{45}Ca detected in the culture medium. The results are expressed as a percentage of ^{45}Ca released from each pair of bones relative to total ^{45}Ca.

The Background Controls (B) are measured to determine the level of spontaneous ^{45}Ca release not attributable to the bPTH (usually about 10 to 15%). The background release value obtained is subtracted from the values obtained for the Test (A) and Untreated Control (D) groups, to give the net % of ^{45}Ca released due to bPTH treatment (the "Net % Untreated" for group D).

The Basal Controls (C) are measured to determine the level of spontaneous ^{45}Ca release inhibition attributable to the test compound at each concentration tested. The basal inhibition values obtained are used as negative controls for the corresponding Test group, subtracting the basal inhibition from the values for each corresponding test group to give a net % of ^{45}Ca bPTH-induced inhibition for each test compound (the "Net % Test").

The results for the overall assay are expressed as mean % inhibition ± sem. of ^{45}Ca released due to test compound treatment (the "% Inhibition"), which is calculated according to the following formula:

$$\frac{\text{Net \% Untreated - Net \% Test}}{\text{Net \% Untreated}} \times 100 = \text{\% Inhibition}$$

The concentration for 50% inhibition (IC_{50}) is also determined.

Compounds of the present invention were tested according to the above-described method and the results are reported below in Table III, demonstrating the ability to inhibit bPTH-induced bone resorption. The

compounds tested were:

A. 2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, prepared, for example, as described in Example 16;

B. 2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, prepared, for example, as described in Example 10 or 13; and

C. 2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, prepared, for example, as described in Example 9 or 11.

Also tested were known anti-bone resorptive agents naproxen, thionaphthene-2-carboxylic acid ("TNCA"), and flurbiprofen ("FBP").

Table III

Compound	Dose	% Inhibition	IC_{50}
Naproxen	$2x10^{-4}$	34.45 ± 8.51	
	$1x10^{-4}$	IA	$>2.0x10^{-4}$
TNCA	$3x10^{-4}$	81.93 ± 3.18	
	$1x10^{-4}$	59.62 ± 4.49	$7.0x10^{-5}$
	$3x10^{-5}$	27.76 ± 11.41	
FBP	$1x10^{-4}$	23.50 ± 16.74	
	$5x10^{-5}$	10.94 ± 9.36	$>1.0x10^{-4}$
A	$1x10^{-4}$	82.73 ± 5.88	
	$5x10^{-5}$	69.23 ± 5.45	$1.8x10^{-5}$
	$1x10^{-5}$	41.84 ± 7.23	
	$5x10^{-6}$	2.28 ± 17.63	
B	$1x10^{-4}$	111.34 ± 6.05	
	$1x10^{-5}$	78.64 ± 8.45	
	$5x10^{-6}$	58.03 ± 11.23	$3.8x10^{-6}$
	$1x10^{-6}$	8.94 ± 14.53	
	$1x10^{-5}$*	78.02 ± 2.96	
	$5x10^{-6}$*	55.99 ± 8.41	$4.3x10^{-6}$
	$1x10^{-6}$*	-10.43 ± 18.36	
C	$1x10^{-4}$	38.07 ± 10.01	$>1.0x10^{-4}$

*Result obtained during a separate run.

EXAMPLE 41
Test for Antipyretic Activity Using Yeast-Induced Fever in the Rat

Antipyretic activity is determined in vivo by the Yeast-induced Fever in the Rat Assay, as is well accepted in the art. A modification of the assay described by Roszkowski, A.P. et al., supra., is performed as follows:

Rats are divided into testing groups, with five animals per group. One group is used as a normal, negative control. Other groups are used as a positive control (yeast + vehicle only), a control with a known effective compound (yeast + control compound, e.g., aspirin in vehicle), and as test groups (yeast + test compound in vehicle). Yeast is injected into all but the negative control group of rats. After 18 hours, the rectal temperature of the rats is measured, test or control compounds are administered orally, and temperature is monitored hourly over a period of three to six hours. Results are interpreted in terms of whether there is a significant decrease (e.g., on the order of about 2°F).

Compounds of the present invention were tested according to the above-described method and the results are reported below in Table IV, demonstrating their antipyretic activity. The compounds tested were:

A. 2-thiocyano-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, prepared, for example, as described in Example 16;

B. 2,4,5-trichloro-3-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, prepared, for example, as described in Example 10 or 13; and

C. 2-chloro-4-(3,5-di-t-butyl-4-hydroxybenzoyl)pyrrole, prepared, for example, as described in Example 9 or 11.

Table IV

Group mg/kg	Temperature °F at Time 0 Hours	1 Hour	2 Hours	3 Hours	4 Hours
-ve	97.6±.5	97.2±.6	97.1±.7	97.6±1.3	97.6±.2
+ve	101.5±.7	101.4±.4	101.3±.8	101.8±.8	101.5±.5
aspirin 100	102.0±.7	99.0±1.7	100.4±.5	100.9±1.1	100.9±.8
A 50	101.5±.7	99.9±.4	98.4±.6	98.0±.7	97.3±.9
B 50	102.3±.3	101.1±.5	100.8±.4	100.0±.8	99.6±1.2
C 50	101.8±.5	99.4±1.0	98.3±1.2	98.3±.9	98.6±.9

EXAMPLE 42
MYOCARDIAL CREATINE KINASE ASSAY

The enzyme activity of creatine kinase is a sensitive indicator os ischemic insult and is relatively specific for myocardial and skeletal tissues (Tanzer and Gilvarg, Creatinine and Creatine Kinase Measurement, J. Biol. Chem., 234, 3201 (1959)). As such, changes in myocardial creatine kinase activity can be used to directly determine the evolution and ultimate extent of myocardial damage following experimental coronary occlusion.

Male Sprague-Dawley rats weighing 250-400 g were anesthetized with a combination of 35 mg/kg ketamine i.m. and 5 mg/kg xylazine, intubated, and ventilated with room air via Harvard Respirator. Myocardial infarction was induced using a modified approach to a procedure

described by Seyle, et al., Simple Techniques for the Surgical Occlusion of Coronary Vessels in the Rat, Angiology, 11, 398-407 (1960). Rats were divided into control and test groups. Drug was suspended in carboxylmethyl cellulose. The drug tested group received 30 mg/kg of compound, p.o. in two doses for three days prior to coronary artery occlusion-reperfusion. In addition compound was administered 2 hours prior to coronary artery occlusion-reperfusion at a dose of 15 mg/kg, p.o. Control animals were correspondingly dosed with vehicle.

Hearts were excised from all surviving animals at their assigned times of sacrifice. The left ventricular free wall and septum were isolated and sliced from apex to base into 2.5 mm thick cross sections. Excluding the apex and base, the three intermediate sections were dried and weighed, and were homogenized in 5 mls of buffered homogenizing solution (100 mM imidazole, 10 mM KCl, pH 6.9). The homogenate was then centrifuged in a Sorvall centrifuge (4°C) for 20 minutes at 20,000 g. The resulting supernatant was diluted 1:51 in saline, and creatine kinase was spectrophotometrically assayed at 340 nm approximately 90 minutes after sacrifice. Tissue enzyme was quantitatively determined at 30°C according to Sigma Procedure 47-UV.

A test of one way variance was used to calculate and compare mean myocardial creatine kinase between and within experimental groups. Myocardial creatine kinase activity was expressed in units per gram myocardium (IU/g) and comparisons were made between normal, reperfused, and ligated groups.

In addition, lactate dehydrogenase activity was also determined using the same preparation as for creatine kinase according to Sigma Procedure 228-UV. A

one way analysis of variance was used to compare the differences in myocardial creatine kinase and lactate dehydrogenase activities within the control and drug treated animals.

Mean data for myocardial creatine kinase activity in each of the groups are presented in Table V. The test compound used is X' wherein R is hydrogen, X Y and Z are chloro, m is 0 and n is 1.

Table V

Group	No. Animals	IU/g ww (mean ± SEM)
control	26	794 ± 28
test	22	876 ± 31*

*p < .056

The effects of the test compound on lactate dehydrogenase activity (IU/g ww Myocardium) following coronary artery occlusion-reperfusion in the rat are given in the following table.

Group	No. Animals	IU/g ww (mean ± SEM)
control	26	177 ± 6.5
test	22	202 ± 7.0*

*p < 0.01

EXAMPLE 43
TOXICOLOGICAL STUDIES

The following compounds of formula X' were submitted for toxicological study:

R is hydrogen, X, Y and Z are chloro, m is 0 and n is 1;

R is hydrogen, X is chloro, Y and Z are hydrogen, m is 0 and n is 1;

R is hydrogen, X is thiocyano, X and Z are hydrogen, m is 0 and n is 1.

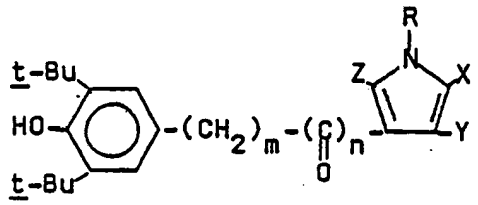
Each of the compounds was administered by gavage daily for 14 days to cynomolgus monkeys. The doses for each compound was 10, 50, and 250 mg/kg/day. Vehicle control groups were also used for the study. No treatment-related effects were seen in the monkeys following gross or microscopic pathology.

No mutagenic activity was seen in the Ames assay conducted on the above three test compounds.

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

CLAIMS FOR ALL CONTRACTING STATES EXCEPT ES :

1. A compound represented by the formula:



or a pharmaceutically acceptable salt thereof wherein:

m is an integer from zero to three;

n is an integer from zero to one;

m+n is an integer from one to three;

R is hydrogen, lower alkyl, carboxy lower alkylene, phenyl or benzyl; and

X, Y and Z are independently selected from hydrogen, lower alkyl, halo, SCN, SR', SOR", SO_2R" and CF_3,

wherein R' is H, aryl, lower alkyl or lower alkanoyl; and R" is lower alkyl.

2. The compound of Claim 1 wherein: m is zero and R is hydrogen.

3. The compound of Claim 1 wherein all non-hydrogen X, Y and Z substituents are identical.

4. The compound of Claim 2 wherein: lower alkyl is methyl or ethyl; halo is chloro or bromo; and lower alkanoyl is acetyl.

5. The compound of Claim 2 wherein: X, Y and/or Z is hydrogen or chloro.

6. The compound of Claim 5 wherein X, Y and Z are chloro.

7. The compound of Claim 5 wherein: X is chloro; and Y and Z are hydrogen.

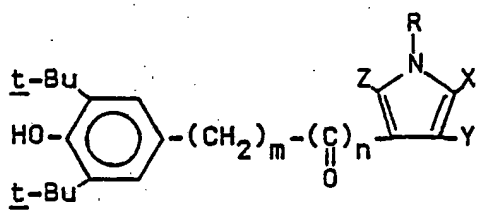
8. The compound of Claim 5 wherein: X, Y and Z are hydrogen.

9. The compound of Claim 2 wherein: X is thiocyano; and Y and Z are hydrogen.

10. The compound of Claim 1 wherein: m is one; n is zero; R is hydrogen; and X, Y and Z are hydrogen.

11. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable carrier.

12. A compound represented by the formula:



or a pharmaceutically acceptable salt thereof wherein:

m is an integer from zero to three;
n is an integer from zero to one;
m+n is an integer from one to three;
R is halo or a removable directing group; and

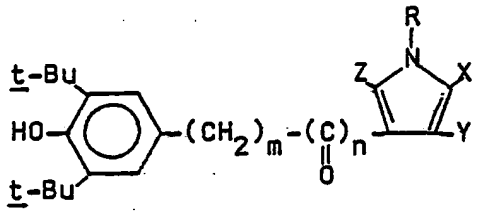
X, Y and Z are independently selected from hydrogen, lower alkyl, trifluoromethyl, halo, SCN and SR',

wherein R' is hydrogen, aryl, lower alkyl or lower alkanoyl.

13. The compound of Claim 12 wherein said removable directing group is selected from the group: arylsulfonyl, aryl lower alkylsulfonyl, lower alkyl arylsulfonyl, lower alkylsulfonyl, and benzoyl.

14. The use of a compound of any one of claims 1 to 10 in the manufacture of a medicament for the treatment of inflammatory diseases, pain, pyrexia, psoriasis, allergic conditions, inflammatory bowel disease, ischemic heart disease, and bone diseases in a mammal.

15. A process for the preparation of compounds of formula X'



or a pharmaceutically acceptable salt thereof wherein:

m is an integer from zero to three;

n is an integer from zero to one;

m+n is an integer from one to three;

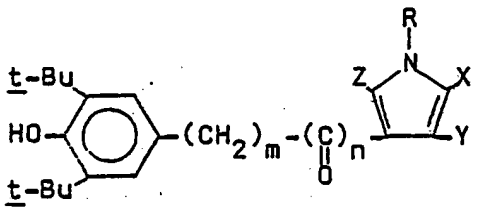
R is hydrogen, lower alkyl, carboxy lower alkylene, phenyl or benzyl; and

X, Y and Z are independently selected from hydrogen, lower alkyl, halo, SCN, SR', SOR", $SO_2R"$ and CF_3,

wherein R' is H, aryl, lower alkyl or lower alkanoyl; and R" is lower alkyl

which comprises

a) reacting a compound of the formula



(Formula X)

wherein:

"t-Bu-" refers to $-C(CH_3)_3$, the tertiary butyl radical;

m is an integer from zero to three;

n is an integer from zero to one;
m+n is an integer from one to three;
R is halo, or a removable directing group; and
X, Y and Z are independently selected from H, lower alkyl, CF_3, halo, SCN, SR', SOR" and SO_2R" (wherein R' is H, aryl, lower alkyl or lower alkanoyl; and R" is lower alkyl or aryl)

with a strong base to form a compound of formula X' wherein R equals hydrogen; or

b) reacting a compound of formula X' wherein R equals hydrogen with the appropriate alkylating agent and an alkali metal hydride to form a compound of formula X' wherein R is lower alkyl, benzyl, phenyl, or carboxy lower alkylene; or

c) reacting a compound of formula X' wherein X, Y, and/or Z is/are hydrogen with thiocyanogen to form a compound of formula X' wherein X, Y, and/or Z is/are a thiocyano group; or

d) reacting a compound of formula X' wherein X, Y, and/or Z is/are a thiocyano group in an alcoholic solution of an inorganic base followed by acidification to form a compound of formula X' wherein X, Y, and/or Z is/are a mercapto group; or

e) reacting a compound of formula X' wherein X, Y, and/or Z is/are a thiocyano group with an alkali iodide followed by a methanolic solution of an inorganic base to form a compound of formula X' wherein X, Y, and/or Z is/are an alkylthio group; or

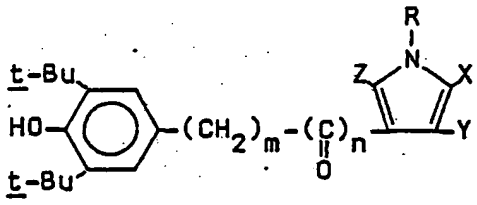
f) reacting a compound of formula X' wherein X, Y, and/or Z is/are a thiocyano group with an alkali metal acetate in an alkanoic acid and an alkanoic anhydride with a strong reducing agent to form a compound of formula X' wherein X, Y, and/or Z is/are a lower alkanoylthio group; or

g) oxidizing a compound of formula X' wherein X, Y, and/or Z is/are an alkylthio or alkylsulfinyl group to form a compound of formula X' wherein X, Y, and/or Z is/are an alkylsulfinyl or alkylsulfonyl group; or

h) reacting a compound of formula X' wherein X, Y, and/or Z is/are hydrogen with a halogenating agent to form a compound of formula X' wherein X, Y, and/or Z is/are halo; or

i) reacting a compound of formula X' wherein n is one with a strong reducing agent to form a compound of formula X' wherein n is zero; or

j) reacting a compound of the formula



or a pharmaceutically acceptable salt thereof wherein:

m is an integer from zero to three;
n is an integer from zero to one;
m+n is an integer from one to three;
R is halo; and
X, Y and Z are halo,

with a strong reducing agent to form a compound of formula X' wherein X, Y, and Z are halo; or

k) reacting a compound of formula X' wherein X and/or Y is/are chloro and Z is chloro with Zinc in acetic acid to form a compound of formula X' wherein Z is hydrogen; or

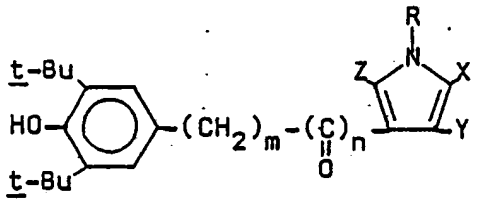
l) partitioning a mixture of compounds of formula X' wherein X is chloro and Y and/or Z is/are chloro between an aqueous base and a chlorinated solvent, to isolate a compound of formula X' wherein X is chloro and Y and Z are hydrogen in the resulting organic phase; or

m) converting a compound of formula X' to its pharmaceutically acceptable salt; or

n) converting a pharmaceutically acceptable salt of a compound of formula X' to the corresponding free compound of formula X'; or

o) converting a pharmaceutically acceptable salt of a compound of formula X' to another pharmaceutically acceptable salt of a compound of formula X'.

16. A process for the preparation of a compound of formula X



(Formula X)

or a pharmaceutically acceptable salt thereof wherein:

"t-Bu-" refers to $-C(CH_3)_3$, the tertiary butyl radical;

m is an integer from zero to two;

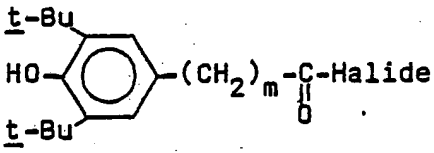
n is one;

m+n is an integer from one to three;

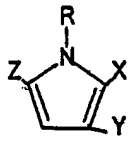
R is halo or a removable directing group; and

X, Y and Z are independently selected from H, lower alkyl, CF_3, halo, SCN, SR', SOR" and SO_2R" (wherein R' is H, aryl, lower alkyl or lower alkanoyl; and R" is lower alkyl or aryl)

which comprises reacting a compound of the formula



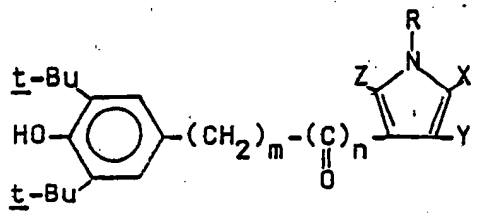
wherein m is as defined above, with a compound of the formula



wherein R, X, Y, and Z are as defined above to form a compound of formula X.

CLAIMS FOR CONTRACTING STATE ES :

1. A process for the preparation of a compound represented by Formula X'



or a pharmaceutically acceptable salt thereof wherein:

m is an integer from zero to three;

n is an integer from zero to one;

m+n is an integer from one to three;

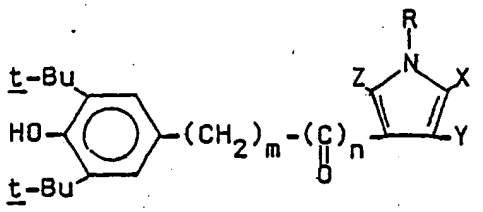
R is hydrogen, lower alkyl, carboxy lower alkylene, phenyl or benzyl; and

X, Y and Z are independently selected from hydrogen, lower alkyl, halo, SCN, SR', SOR", SO_2R" and CF_3,

wherein R' is H, aryl, lower alkyl or lower alkanoyl; and R" is lower alkyl

which comprises

a) reacting a compound of the formula



(Formula X)

wherein:

"t-Bu-" refers to $-C(CH_3)_3$, the tertiary butyl radical;

m is an integer from zero to three;

n is an integer from zero to one;
m+n is an integer from one to three;
R is halo, or a removable directing group; and
X, Y and Z are independently selected from H, lower alkyl, CF_3, halo, SCN, SR', SOR" and $SO_2R"$ (wherein R' is H, aryl, lower alkyl or lower alkanoyl; and R" is lower alkyl or aryl)

with a strong base to form a compound of formula X' wherein R equals hydrogen; or

b) reacting a compound of formula X' wherein R equals hydrogen with the appropriate alkylating agent and an alkali metal hydride to form a compound of formula X' wherein R is lower alkyl, benzyl, phenyl, or carboxy lower alkylene; or

c) reacting a compound of formula X' wherein X, Y, and/or Z is/are hydrogen with thiocyanogen to form a compound of formula X' wherein X, Y, and/or Z is/are a thiocyano group; or

d) reacting a compound of formula X' wherein X, Y, and/or Z is/are a thiocyano group in an alcoholic solution of an inorganic base followed by acidification to form a compound of formula X' wherein X, Y, and/or Z is/are a mercapto group; or

e) reacting a compound of formula X' wherein X, Y, and/or Z is/are a thiocyano group with an alkali iodide followed by a methanolic solution of an inorganic base to form a compound of formula X' wherein X, Y, and/or Z is/are an alkylthio group; or

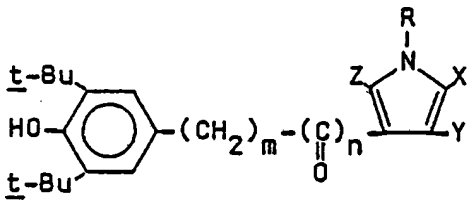
f) reacting a compound of formula X' wherein X; Y, and/or Z is/are a thiocyano group with an alkali metal acetate in an alkanoic acid and an alkanoic anhydride with a strong reducing agent to form a compound of formula X' wherein X, Y, and/or Z is/are a lower alkanoylthio group; or

g) oxidizing a compound of formula X' wherein X, Y, and/or Z is/are an alkylthio or alkylsulfinyl group to form a compound of formula X' wherein X, Y, and/or Z is/are an alkylsulfinyl or alkylsulfonyl group; or

h) reacting a compound of formula X' wherein X, Y, and/or Z is/are hydrogen with a halogenating agent to form a compound of formula X' wherein X, Y, and/or Z is/are halo; or

i) reacting a compound of formula X' wherein n is one with a strong reducing agent to form a compound of formula X' wherein n is zero; or

j) reacting a compound of the formula



or a pharmaceutically acceptable salt thereof wherein:

m is an integer from zero to three;
n is an integer from zero to one;
m+n is an integer from one to three;
R is halo; and
X, Y and Z are halo,

with a strong reducing agent to form a compound of formula X' wherein X, Y, and Z are halo; or

k) reacting a compound of formula X' wherein X and/or Y is/are chloro and Z is chloro with Zinc in acetic acid to form a compound of formula X' wherein Z is hydrogen; or

l) partitioning a mixture of compounds of formula X' wherein X is chloro and Y and/or Z is/are chloro between an aqueous base and a chlorinated solvent, to isolate a compound of formula X' wherein X is chloro and Y and Z are hydrogen in the resulting organic phase; or

m) converting a compound of formula X' to its pharmaceutically acceptable salt; or

n) converting a pharmaceutically acceptable salt of a compound of formula X' to the corresponding free compound of formula X'; or

o) converting a pharmaceutically acceptable salt of a compound of formula X' to another pharmaceutically acceptable salt of a compound of formula X'.

2. The process of Claim 1 wherein a compound is prepared in which m is zero and R is hydrogen.

3. The process of Claim 1 wherein a compound is prepared in which all non-hydrogen X, Y and Z substituents are identical.

4. The process of Claim 2 wherein a compound is prepared in which lower alkyl is methyl or ethyl; halo is chloro or bromo; and lower alkanoyl is acetyl.

5. The process of Claim 2 wherein a compound is prepared in which X, Y and/or Z is hydrogen or chloro.

6. The process of Claim 5 wherein a compound is prepared in which X, Y and Z are chloro.

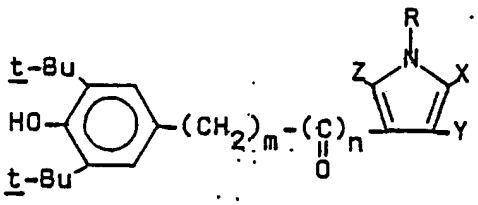
7. The process of Claim 5 wherein a compound is prepared in which X is chloro; and Y and Z are hydrogen.

8. The process of Claim 5 wherein a compound is prepared in which X, Y and Z are hydrogen.

9. The process of Claim 2 wherein a compound is prepared in which X is thiocyano; and Y and Z are hydrogen.

10. The process of Claim 1 wherein a compound is prepared in which m is one; n is zero; R is hydrogen; and X, Y and Z are hydrogen.

11. A process for the preparation of a compound of formula X



(Formula X)

or a pharmaceutically acceptable salt thereof wherein:

"t-Bu-" refers to $-C(CH_3)_3$, the tertiary butyl radical;

m is an integer from zero to two;

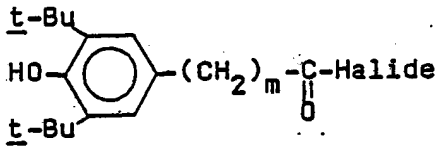
n is one;

m+n is an integer from one to three;

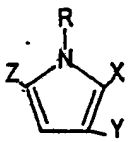
R is halo or a removable directing group; and

X, Y and Z are independently selected from H, lower alkyl, CF_3, halo, SCN, SR', SOR" and SO_2R" (wherein R' is H, aryl, lower alkyl or lower alkanoyl; and R" is lower alkyl or aryl)

which comprises reacting a compound of the formula



wherein m is as defined above, with a compound of the formula



wherein R, X, Y, and Z are as defined above to form a compound of formula X.

12. The process of Claim 11 wherein a compound is prepared in which said removable directing group is selected from arylsulfonyl, aryl lower alkylsulfonyl, lower alkyl arylsulfonyl, lower alkylsulfonyl, and benzoyl.

13. The use of a compound prepared in accordance with any one of claims 1 to 10 in the manufacture of a medicament for the treatment of inflammatory diseases, pain, pyrexia, psoriasis, allergic conditions, inflammatory bowel disease, ischemic heart disease and bone diseases in a mammal.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 87 11 7332

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.3)
A,D	CHEMICAL & PHARMACEUTICAL BULLETIN, vol. 32, no. 1, January 1984, pages 152-165; Y. ISOMURA et al: "Synthesis and anti-inflammatory activity of 2,6-di-tect-butylphenols with a heterocyclic group at the 4-position. III" * table III, compound no. 15 *	1,11,14	C 07 D 207/333 C 07 D 207/34 C 07 D 207/36 C 07 D 207/46 C 07 D 207/48 A 61 K 31/40
A	PATENT ABSTRACTS OF JAPAN, vol. 7, no. 268 (C-197)[1413], 30th November 1983; & JP - A - 58 148 858 (YAMANOUCHI SEIYAKU K.K.) 05-09-1983	1,11,14	
A	PATENT ASBTRACTS OF JAPAN, vol. 9, no. 166 (C-290)[1889], 11th July 1985; & JP - A - 60 38361 (MEIJI SEIKA K.K.) 27-02-1985	1,12,15 ,16	
A,D	US-A-3 644 631 (I.J. PACHTER et al.) * column 1, line 30 - column 3, line 46 *	1,11,14	TECHNICAL FIELDS SEARCHED (Int. Cl.3)
A	WO-A-8 301 774 (RIKER LABORATORIES INC.) * claims * & US - A - 4 418 074 (Cat. D)	1,11,14	C 07 D 207/00 A 61 K 31/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	29-02-1988	VAN AMSTERDAM L.J.P.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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